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STEATORRHOEA IN THE ADULT*

BY

J. BADENOCH, D.M., F.R.C.P.

Consultant Physician, United Oxford Hospitals

My interest in this subject stems from two main sources. Firstly, after the war I was privileged to work in Professor Witts's department in Oxford, where the main lines of study have been in haematology and gastro-enterology, and patients with one or other of the malabsorption syndromes forged a link between these two and lay at the focal point of our research. Secondly, it seemed to me that clinically the steatorrhoeas marched across the whole field of medicine and surgery in the way that syphilis used to do in the old days, and there was hardly a special department which could not produce a number of cases from its records.

Steatorrhoea is a convenient marker of small-intestinal insufficiency, but we now know that the condition is one of panmalabsorption, and it is this universal failure of function which gives rise to the wide variety of symptoms and signs and makes the condition so interesting to physicians in all branches of medicine.

My purpose in these lectures is to present the clinical picture of steatorrhoea as I have seen it in Oxford, to survey the widely differing conditions which may lead to its development, and to use this framework to indicate the present limits of our knowledge.

A Retrospective Glance

But let us first look back at the origins of our subject. The classical and mediaeval physicians, with their great interest in urinoscopy and excreta generally, could hardly fail to have been struck by the cardinal signs of steatorrhoea. Indeed, Aretaeus the Cappadocian, who practised possibly in Rome in the second century A.D., has left us an account of a disease which closely resembles the clinical picture of steatorrhoea as we know it to-day (Adams, 1856). He writes: "In the coeliac affection the heat does not digest the food nor convert it into its proper chyme but leaves its work half unfinished. The food then being deprived of this operation is changed to a state which is bad in colour as well as consistence. For its colour is white and without bile and it is liquid from no part of the digestive process having been properly done except the commencement."

This has an authentic ring about it, and how interesting it is to learn that even in classical times research had its problems; for the scholars tell us that Aretaeus may well have copied this account from an earlier authority, possibly Archiagenes, without acknowledging his debt.

1,500 years later, in 1669, Vincent Ketelaer, a Dutch physician who was rector of the Gymnasium at Zierickzee, published a treatise in which he described cases of stomatitis which were occurring in the Low Countries. The lesions in the mouth were accompanied by a phalanx of symptoms, among them a most pernicious diarrhoea which left behind scarcely any juice for the body, with faeces so voluminous that several basins could scarcely hold them (Hanes, 1938).

From the descriptions of the classical diarrhoea, there seems little doubt that both Aretaeus and Ketelaer were describing patients with steatorrhoea, but it was not until 1776 that William Hillary gave the first clear account of the sprue syndrome. In his *Observations on the Changes of the Air and the Concomitant Epidemical Diseases in the Island of Barbados* he described the pallor and emaciation of the sufferers, the soreness of the mouth, and the diarrhoea with pale foul stools, and noted that the disease pursued a relapsing course and often proved fatal. In 1864 Julien, working in the French Colonies in Asia, stated his belief that the "diarrhoea alba," or Cochin China dysentery as it was then known, was a specific condition different from other forms of dysentery. Finally, in 1880, van der Berg in Java and Manson in China, writing independently, described the disease which Hillary had observed a century before and defined it as a distinct clinical entity.

By the end of the last century many physicians practising in the tropics had become familiar with sprue and were adding to our knowledge of it, and yet the fact that there was a curiously similar condition occurring in the home countries of Europe went unremarked. It is true that both Aretaeus and Ketelaer had described cases with bulky diarrhoea, but in modern times no further description appeared until Samuel Gee (1888) published his classical paper on the coeliac affection. In four short pages he gives an account which will stand comparison with any written to-day. He described the natural history of the disease as slow with a relapsing course, sometimes fatal, often leaving the children weak and stunted even if recovery took place. He mentioned that occasionally Englishmen returned from India sick with the coeliac affection and that seldom it was met with in adults who had never left this island. At necropsy he could find nothing to explain the severity of the condition, and his paper ends with the prophetic statement that "if the patient can be cured at all it shall be by means of diet." One can imagine how interested he must have been when a child who was fed upon a quart of the best Dutch mussels daily throve wonderfully, but relapsed when the season for mussels was over. Unhappily the controlled experiment was incomplete, because the next season the child could not be prevailed upon to eat the mussels again.

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To-day, as in the time of Gee himself, the nature of the fundamental defect in the absorption of fat still eludes us, but, as I hope to show, our knowledge of the causes of steatorrhoea and the pathogenesis of its clinical signs and symptoms has grown rapidly in recent years, and it may not be long before the final door yields to the steady pressure which is being put upon it.

Present Investigation

In Oxford I have had the opportunity to study 163 patients with steatorrhoea (Table I).

TABLE I.—*Number of Patients Studied*

Idiopathic steatorrhoea (onset in childhood 32)	106
Regional ileitis	11
Pancreatic disease	8
Gastric operations	8
Diverticulosis of the jejunum	8
Tropical sprue	7
Tabes mesenterica	4
Blind loops of intestine	3
Gastro-colic+ileo-colic fistulae	2
Mesenteric thrombosis	2
Whipple's disease	1
Unclassified	3
Total	163

The majority, 106, were suffering from idiopathic steatorrhoea, and in the remainder the failure of fat absorption was due to a variety of other causes. The three unclassified cases provided insufficient data for a certain diagnosis.

About one-third of the patients in the idiopathic group first developed their symptoms in childhood and are probably cases of coeliac disease whose symptoms have continued into adult life. Ten years ago I would have defined the remainder of these with confidence as a single entity. Now I am not so sure. The difficulty is that, traditionally, idiopathic steatorrhoea has been a diagnosis that is made by exclusion. It is what is left when all other possible causes have been eliminated. In the past two years new methods of study, particularly the peroral biopsy of the mucosa of the small intestine, has enabled the diagnosis to be made with greater precision. Already it appears that while some, probably the majority, of the cases of idiopathic steatorrhoea are in fact adult cases of coeliac disease, as their response to the gluten-free diet would suggest, yet the pathological changes in the intestine may not be the same in all, and there may be more than one cause for the breakdown in function.

Nevertheless, it is convenient for the moment to consider them as a clinical group, so long as this does not imply a common aetiology which is not yet proved, or suggest that the dangerous deficiencies which may arise are limited to the idiopathic cases. This view, widely held in the past, has prevented the acceptance of the fact that a crippling osteomalacia may accompany chronic pancreatitis or that subacute combined degeneration of the cord may follow an intestinal anastomosis for Crohn's disease.

In the 74 patients with idiopathic steatorrhoea, whose illness began after childhood, symptoms most commonly developed between the ages of 30 and 39 (Table II). If, as appears to be the case, most of these patients are suffering from an adult form of coeliac disease, it seems curious to me that the majority do not break down in adolescence or early adult life, but do so in the fourth and fifth decades, when the major metabolic demands of growth and child-bearing are on the wane. In patients with other forms of steatorrhoea the age of onset varied with the underlying disease. In every series the presenting symptoms depend in large measure on the way in which the cases are collected, and perhaps my own have a bias because of our special interest in the anaemias.

TABLE II.—*Age at Onset of Symptoms of 74 Patients with Idiopathic Steatorrhoea*

Age in years	10–19	20–29	30–39	40–49	50–59	60–69	70–79
No. of patients	4	12	25	19	10	3	1

On the other hand, my findings emphasize once again the danger of putting too much reliance on the disturbance of the bowels (Table III). In 106 patients with idiopathic steatorrhoea tiredness or breathlessness were as common as diarrhoea as a presenting symptom, and a significant number mentioned that soreness of the tongue occurred long before other symptoms developed.

TABLE III.—*Presenting Symptoms of 106 Patients with Idiopathic Steatorrhoea*

Tiredness or breathlessness	38
Diarrhoea	35
Soreness of the tongue	12
Indigestion	10
Flatulence	6
Dermatitis	3
Heart failure	1
Rectal haemorrhage	1

Most of the patients are underweight and small in stature, and this is particularly true of those in whom the disease dates from childhood. Possibly because we are close to some good galloping country, steatorrhoea has become known locally in Oxford as the jockey's disease—there were five in this series; and more than once I have been accused of spoiling a promising future by making a young man grow again.

Usually the diagnosis of steatorrhoea is easy. The classical patient with pallor, wasted limbs, and distended belly, complaining of diarrhoea with large, pale, foul stools and soreness of the tongue could hardly be missed. But we have learnt that many patients with impaired fat-absorption have normal bowel habits and pass formed stools of normal colour, and in these the diagnosis may be overlooked until a near disaster has occurred. No fewer than 11 out of the 163 patients in this series denied that they had ever had any significant disturbance of the bowels; but in three of these, although the bowels were opened once daily and the patient thought his stools were normal, the ward sister commented on their size and pallor.

The most common gastro-intestinal symptoms are diarrhoea, flatulence, and abdominal distension. Although usually the diarrhoea is relatively painless, this is not always the case, and in some patients attacks of subacute intestinal obstruction produce violent colic and may endanger life. This occurred in 15 patients in my series (Table IV), and if we exclude the five with regional ileitis who had organic strictures, there remain 10 who suffered from recurrent colic with distended loops of bowel without obvious permanent narrowing of the lumen of the gut. Three of them died as a result of volvulus. This syndrome of chronic obstruction has multiple causes. In the absence of organic stricture it may depend on the disorder of motor function that seems common in patients with jejunal diverticulosis,

TABLE IV.—*Incidence of Intestinal Obstruction. Figures in Parentheses Indicate the Number of Patients in Each Group in the Series*

Regional ileitis (11)	5
Diverticulosis of jejunum (8)	5
Idiopathic steatorrhoea (106)	2
Partial gastrectomy (8)	1
Tabes mesenterica (4)	1
Mesenteric thrombosis (2)	1

on impairment of the blood supply, possibly on disturbed autonomic control as in the patient recently described by Naish and Capper (1960), or on the impaction, in widely dilated bowel, of a mass of pultaceous contents which cannot be moved on by peristalsis.

Loss of Vitamins

Steatorrhoea due to any cause may lead to loss of the fat-soluble vitamins A, D, E, and K in the stools. Clinical deficiency of vitamin A is rare, and I have no definite examples in my series, although lack of the vitamin may have contributed to the dryness and hyperkeratosis of the skin which is often noted, and to the reduced resistance to infection. Similarly, deficiency of vitamin E must occur, and in patients coming to necropsy we have seen a brown pigment in the muscle layers of the intestine and elsewhere which has been attributed to a deficiency of the vitamin. On the other hand, there are no clinical signs which could be attributed to lack of vitamin E. The obstetric history of patients with steatorrhoea on full vitamin supplements, with the exception of vitamin E, is normal, and my efforts to relieve muscular weakness and wasting with large doses of the vitamin have been without avail.

In considering the lack of vitamin D, I am on much firmer ground. In this series, osteomalacia of sufficient degree to cause skeletal pain occurred in 26 patients (Table V).

TABLE V.—*Incidence of Osteomalacia. Figures in Parentheses Indicate the Number of Patients in Each Group in the Series*

Idiopathic steatorrhoea (106)	20
Regional ileitis (11)	2
Partial gastrectomy (8)	1
Tabes mesenterica (4)	1
Diverticulosis of jejunum (8)	1
Pancreatic disease (8)	1

Twenty of them were in the idiopathic group, but the condition was not limited to steatorrhoea due to disease of the intestine, it also occurred after partial gastrectomy and in pancreatic steatorrhoea where the prime fault lies in fat-digestion. Many of these cases are tragic. Widespread skeletal pain, the absence of true arthritis, and the failure of our usual remedies for muscular strain, often brand the patient as neurotic for years before the correct diagnosis is made. Rapid growth in adolescence or the strain of pregnancy may precipitate symptoms and the cause of the steatorrhoea is unimportant, for softening of the bones may occur whenever fat-absorption is impaired. Not all have diarrhoea or pale, bulky stools, and these patients with osteomalacia, without other symptoms suggesting malabsorption, form one of the most important occult groups among the steatorrhoeas.

Role of Hypocalcaemia

A great deal of interest continues to be focused on the cause of the bone disease in steatorrhoea. The classical theory (Fig. 1) was that the absorption of calcium was impaired, partly because of a deficiency of vitamin D and partly because the calcium itself was lost in the stools in the form of insoluble soaps of fatty acid. This led to a negative calcium balance and a fall in blood calcium. In a proportion of cases tetany occurred, but in the remainder the parathyroids responded to the stimulus and a secondary hyperparathyroidism raised the calcium in the blood to safer levels at the expense of the bones. As Davies, Dent, and Willcox (1956) have shown, this secondary hyperparathyroidism may proceed to the length of tumour formation, and the resulting adenomata may have to be removed surgically before the softening of the bones can be halted. In the elderly, in post-menopausal women, and in the presence of gross malnutrition, disturbance of the protein matrix of the bone and osteoporosis may complicate the picture still further.

This classical theory may require modification in the future. It has been shown by Nassim and his colleagues that the calcium balance does not correlate well with the degree of steatorrhoea, possibly because of variation in the activity of the parathyroids (Nassim, Saville, Cook, and Mulligan, 1959), or because of changes in the volume, and hence in the calcium contents of the large quantities of digestive juices which are poured into the lumen of the gut.

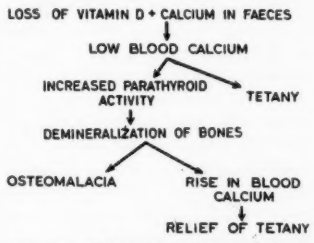

FIG. 1.—Pathogenesis of osteomalacia and tetany in patients with steatorrhoea.

Whatever the cause of the failure to absorb calcium, it is clear that some patients will respond to vitamin D and others will not, whether the vitamin is given orally or parenterally. I believe that in our thinking about this problem we have been guilty of falling into a trap, similar to the one that beset us in our studies of the absorption of vitamin B_{12} in steatorrhoea. Knowing that vitamin D is involved in the normal absorption of calcium, we are prone to believe that it is this specific mechanism that has broken down in the malabsorption syndromes. In fact, if we assume that this is not the sole explanation we are more likely to make progress.

As long ago as 1931, Marble and Bauer showed that the absorption of calcium in steatorrhoea could be improved by treatment with liver alone. To-day there is good evidence that in idiopathic steatorrhoea a gluten-free diet or treatment with steroids will promote absorption of calcium when vitamin D has failed, presumably by removing some other barrier to transfer across the wall of the intestine (MacKay and Volwiler, 1955; Buchan, Marko, and Gerrard, 1958). That this double mechanism is operative is emphasized, firstly, by the fact that the response to steroids is far too rapid to be the result of increased absorption of vitamin D (MacKay and Volwiler, 1955), and, secondly, by the demonstration that the serum of some patients with steatorrhoea and hypocalcaemia has normal antirachitic activity, suggesting that the low blood calcium cannot be due to lack of vitamin D (Morgan, quoted by Morse, Dickson, Nonamaker, and Embree, 1959).

The Parathyroids

It has been accepted that in some of these patients failure to absorb calcium leads to a fall in blood levels and tetany, but in others the parathyroids react to the stimulus and raise the blood calcium at the expense of the stores of calcium and phosphorus in the bones. If this occurs in some, why not in all? So far as I know there is no adequate explanation for this difference, but Bensley and Cameron (quoted by Morse *et al.*, 1959), have suggested that in some patients with steatorrhoea there is a diminished phosphaturic response to injections of parathormone, and it may be that in patients with steatorrhoea and tetany some inhibitor of parathyroid function is present.

There are other links between the parathyroids and steatorrhoea that are even less well understood. Some patients with hypoparathyroidism have steatorrhoea (Lowe, Ellinger, Wright, and Stauffer, 1950; Salvesen and Böe, 1953), and the failure of fat-absorption is not always due to infection of the bowel with yeasts, as was first thought to be the case. Sometimes the steatorrhoea precedes the failure of parathyroid function, and possibly both are the result of a common genetic defect.

Whatever its cause, the fall in blood calcium in steatorrhoea, in addition to producing tetany, may provoke mental disorientation and fits, as in the case described by Kant and Lubing (1947), and it is possible that protracted hypocalcaemia may contribute to the resistance to treatment of some of the skin lesions.

Haemorrhage in Steatorrhoea

Haemorrhage due to lack of vitamin K occurred in 17 patients in my series (Table VI), and, as with osteomalacia, it was not limited to those with idiopathic steatorrhoea. Considering that the haemorrhage may

TABLE VI.—*Incidence of Haemorrhage Due to Deficiency of Vitamin K. Figures in Parentheses Indicate the Number of Patients in Each Group in the Series*

Idiopathic steatorrhoea (106)	13
Regional ileitis (11)	2
Tabes mesenterica (4)	1
Whipple's disease (1)	1

be disastrous, it is odd that it should have been overlooked by so many of the earlier writers. At first it was attributed to scurvy, but it soon became clear that this could not explain the tendency to bleed in every case. In 1927 Fanconi described three patients with a haemorrhagic diathesis which he felt must be due to some other cause. The coagulation time was prolonged and the clot retraction and platelet count were normal, and he concluded that the condition was allied to haemophilia. Eleven years later, when vitamin K had been discovered (Fanconi, 1938), he re-entered the lists and suggested that a deficiency of the vitamin might be the cause of the bleeding in steatorrhoea.

Purpura in the skin is the most common manifestation, but epistaxis, menorrhagia, haematuria, and melaena also occur, and in one of my patients, a man of 67, a sharp rectal haemorrhage was the presenting symptom of the disease. Most dangerous of all, the defect in coagulation may give rise to massive retroperitoneal haemorrhage simulating an acute abdominal catastrophe. I have seen two of these in the past year in patients who had not been under regular treatment, but mercifully the hospital notes provided the diagnosis in both before the surgeon operated in the face of incoagulable blood. In neither was there any external bleeding to suggest the cause of the acute abdominal symptoms and the collapse.

It is well recognized that much of the vitamin K required by man is synthesized within the lumen of the intestine. In patients with steatorrhoea, who may be in a precarious balance, an oral antibiotic may precipitate clinical deficiency by destroying the organisms which synthesize the vitamin within the gut (Heyeraas, 1949).

Glossitis and Dermatitis

Glossitis and dermatitis are prominent symptoms of the malabsorption syndrome. In this series 118 patients complained of soreness of the tongue at some time in the course of their illness, and in 12 it was the presenting symptom, while dermatitis occurred in 15 and

TABLE VII.—*Incidence of Glossitis and Dermatitis in Series of 163 Patients*

Soreness of the tongue	118
Presenting symptom	12
Dermatitis	15
Presenting symptom	3

antedated all other symptoms in 3 (Table VII). Traditionally these symptoms, and also the peripheral neuritis which occurs, have been ascribed to deficiencies of the B group of vitamins, but the picture is not nearly so clear-cut as it is, for example, in the haemorrhagic diathesis due to lack of vitamin K. It can be assumed that, in keeping with other water-soluble substances, the absorption of the B vitamins is impaired, or at least grossly delayed; but attempts by Girdwood (1956) to demonstrate this, in the case of pyridoxine, riboflavine, and aneurine, were unsuccessful.

The second prop in the traditional argument is that, as many of these vitamins are synthesized within the lumen of the intestine in man, the abnormal bacteria assumed to be present in the upper gut in steatorrhoea either use them for their own metabolism or outgrow others on which their synthesis depends.

It may well be that this is the case in steatorrhoea associated with blind loops, or other anatomical abnormalities, in which the upper bowel is known to be teeming with organisms; but attempts to demonstrate bacterial invasion of the small intestine in coeliac disease and idiopathic steatorrhoea have been unconvincing (Gardner, 1957; Anderson and Langford, 1958).

Although vitamin B deficiency due to impaired absorption or bacterial competition may play a part in producing the dermatitis or the neuropathy, proof is lacking that this is the whole explanation. For example, peripheral neuropathy which responds to vitamin B_1 does occur in association with steatorrhoea, yet there are similar cases which progress to the point of incapacity in spite of full doses of all the known vitamins. Clearly other mechanisms must be involved, and the knowledge that lack of calcium can cause resistant eczema, and iron deficiency produce glossitis, suggests that there may be other deficiencies not connected with the vitamins of the B group which may be important. One of these may be lack of protein, for skin lesions are common in nutritional protein deficiencies in the tropics, and Leitner (1958) has described two interesting patients with severe protein malnutrition which followed gastric and pancreatic resections, who suffered from intractable dermatitis.

Moreover, the lesions need not be the result of a lack of a specific factor. They could be due to the absorption of toxic substances formed within the lumen of the intestine. That this can happen is illustrated by the observations of England, French, and Rawson (1960), who studied a patient with Whipple's disease and a light-sensitive dermatitis with excess of porphyrins in the stools. Sterilization of the gut with a broad-spectrum antibiotic led to a fall in the porphyrin excretion and a rapid cure of the dermatitis. Presumably the antibiotic had exerted its effect by destroying the organisms within the lumen of the intestine which were producing the toxic porphyrins.

If the glossitis and dermatitis are due to poor absorption of the B vitamins, it is curious that frank deficiency of the other important water-soluble vitamin, vitamin C, is so rare in steatorrhoea. Only one of the 163 patients in this series had clinical scurvy, and she is an elderly woman in whom a poor diet seemed to be playing the major part in producing the deficiency. It is true that

the level of ascorbic acid in the leucocytes is often low, and it may be that subclinical scurvy plays a part in producing the irritability and swings of mood of which these patients complain; but although the vitamin may be destroyed rapidly if the upper bowel is infected (Kendall and Chinn, 1938), the available evidence suggests that it can be absorbed without much difficulty in the presence of steatorrhoea (Boscott and Cooke, 1954).

Loss of Weight

Loss of weight is common in steatorrhoea, and 76% of the patients in this series who were weighed when they were first seen were one stone (6.4 kg.) or more below their optimum weight. This loss of weight depends partly on the diminished intake of food and partly on the loss of fat and other essential nutriments in the stools. Even amino-acids are poorly absorbed, and some of them may be involved in a breakdown of intermediary metabolism as well. Butterworth, Santini, and Perez-Santiago (1958) have shown that the level of serine in the blood in patients with steatorrhoea is abnormally high. They could not explain this finding, but serine is deaminated by a specific enzyme which requires pyridoxyl phosphate as its coenzyme, and in the presence of a deficiency of pyridoxine the process might be halted. Similarly the excess of *p*-hydroxyphenyl acetic acid, which is found in the urine, may depend on a disturbance of tyrosine metabolism resulting from lack of vitamin C (Boscott and Cooke, 1954).

In many patients the levels of plasma proteins are reduced, but it is probable that diminished absorption does not explain the fall in every case. Protein synthesis may also be disturbed, as is shown by the abnormal electrophoretic pattern. There may be a rise in the β-globulin and sometimes the γ-globulin, and a low albumin in the absence of proteinuria or overt hepatic damage (Adlersberg, Wang, and Bossak, 1957). Moreover, the results of studies on copper metabolism in steatorrhoea have indicated that the specific carrier protein, coeruloplasmin, is poorly synthesized (Butterworth, Gubler, Cartwright, and Wintrobe, 1958). Further evidence of disturbed protein synthesis is provided by the association of impaired fat-absorption with all forms of agammaglobulinaemia, both congenital and acquired (Firkin and Blackburn, 1958). The steatorrhoea usually develops after the abnormality in the plasma proteins, and has been ascribed, on too slender evidence, either to secondary infection of the gut or to blockage of the lymphatics of the mesentery by the underlying lymphomatous process. However, sometimes the steatorrhoea precedes the development of the hypogammaglobulinaemia, and in these patients no adequate explanation for the association has been put forward.

Finally, not only poor absorption and faulty synthesis, but also increased loss of protein into the gastro-intestinal tract may be important. Schwartz and Jarnum (1959) and Young, Levin, Fowler, and Miles (1959) have described cases with steatorrhoea and hypoproteinaemia in which studies with albumin and polyvinylpyrrolidone (P.V.P.), labelled with radioactive iodine, have revealed a very rapid turnover of albumin and considerable losses of protein into the gastro-intestinal tract. The use of radio-iodinated P.V.P. as a marker for protein loss into the bowel represents a very real advance, and should prove most useful in the study of other patients with hypoproteinaemia due to unknown cause.

Some years ago our interest was aroused by a patient with access to the ward scales, who demanded to know why, although he had not had his bowels open during the night, he was invariably 2 lb. (0.9 kg.) lighter in the morning than he had been when he went to bed. In fact, he was giving forthright expression to the observation, made by Wollaeger and Scribner (1951), that patients with steatorrhoea excrete large volumes of water during the night. Wollaeger believed that this was the result of delayed absorption of water drunk during the previous day, and that the delay depended on the presence of food within the lumen of the gut. Jackson, Linder, and Berman (1951), in their classical experiments on their patient with massive resection of the bowel, noted a similar delay in diuresis, but they doubted if slow absorption could be the explanation, because the same effect was noted if the water load was given intravenously. Later, Taylor (1955) showed that the delay in absorption could not be due to the presence of unabsorbed food within the bowel, because it occurred even if the subjects were fasting.

The picture is a complicated one. Higgins, Lee, Scholer, Reitemeier, Code, and Wollaeger (1957), using isotopically labelled water, have shown that absorption is slower than normal in steatorrhoea, but this does not account for the delay in diuresis. Flear, Cooke, and Quinton (1959) showed that fluid taken in the mornings in a fasting state, or with food, gave rise to a delayed diuresis the following night, but that if the same water load was administered to the same patients in the evening it was promptly excreted. They postulate that the nocturnal diuresis that occurs in patients with steatorrhoea is due to an inversion of the normal rhythm of excretion such as has been noted in congestive cardiac failure and cirrhosis of the liver.

Dehydration, weakness, and hypotension are common in all forms of steatorrhoea, and if the asthenia is accompanied by pigmentation of the skin difficulties in diagnosis may arise.

One of the patients in this series, a man aged 44, was admitted to the Radcliffe Infirmary under the care of Dr. A. M. Cooke in 1951. His main complaint was of great weariness; he had lost weight and had abdominal pain and diarrhoea. There was pigmentation of his skin and even of the mucous membranes of his mouth, and his blood-pressure was 90/50. He had been diagnosed as suffering from Addison's disease at another hospital, and both eucortone and D.C.A. had been given without effect. Clinically, he presented the picture of adrenal failure, but the appearance of his stools, which were silver-grey in colour, at once suggested the correct diagnosis and led to effective treatment.

The striking resemblance of some patients with steatorrhoea to sufferers with Addison's disease and the knowledge that the adrenal cortex may play a part in the normal process of fat-absorption have led in the past to repeated suggestions that adrenal cortical failure might be the cause of steatorrhoea (Gloor, 1930; Thaysen, 1932). Although patients severely ill with steatorrhoea and malnutrition may show a functional adrenal insufficiency, all the evidence points to the fact that the asthenia, hyponatraemia, and hypotension that are often encountered are not due to this cause. Prunty and Macoun (1943) have shown that sodium is retained normally by the kidneys in these patients, and Black (1946) demonstrated that replenishing the body stores

of sodium will restore well-being and raise the blood-pressure to normal without need of other measures.

The common occurrence of hypotension has aroused interest. It has been suggested that it might be due to failure of absorption of some substance necessary for the maintenance of normal blood-pressure (Salvesen, 1953). However, although a low blood-pressure is often found when the patient is ill, it is not invariable, and two of my patients had diastolic pressures of over 120 mm. of mercury during the course of their illness.

Potassium Depletion

For many years it has been known that patients with steatorrhoea could suffer from profound muscular weakness. In the records of the Radcliffe Infirmary we have the story of one patient who died of what was thought to be a creeping paralysis, which progressed to such an extent that terminally she was unable to lift her head from the pillow. At the time the cause of her distress was unknown, but Harrison, Tompsett, and Barr (1943) showed that the weakness of patients with steatorrhoea was often due to the loss of large amounts of potassium in the stools, and that supplements of the mineral would bring about improvement in muscle power. The loss of potassium parallels the bulk of the stool and it can be quite large even if the stools are semi-formed (Cooke, Thomas, Mangall, and Cross, 1953).

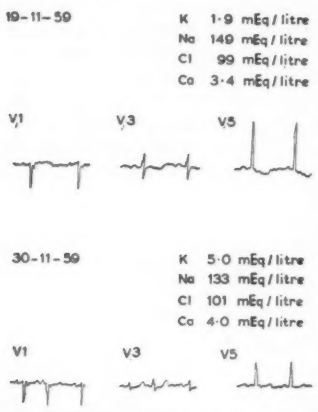

FIG. 2.—Electrolyte levels in blood and electrocardiograph of a patient with steatorrhoea and severe muscular weakness before (November 19, 1959) and after (November 30, 1959) supplements of potassium were given.

Fig. 2 shows the serum levels of electrolytes and the electrocardiographic findings in a patient with steatorrhoea who had profound muscular weakness due to hypokalaemia.

Before treatment was begun the level of potassium was low and the electrocardiogram showed the sagging ST segments and prominent U waves of hypokalaemia. When potassium supplements were given, her weakness improved, and the electrocardiographic trace became more normal.

Potassium depletion used to be one of the most dangerous complications of the malabsorption syndrome, and it was responsible for many deaths before its importance was realized. Apart from producing muscular weakness, it may contribute to atony of the bowel and abdominal distension, and may mask tetany due to low blood calcium. More than once I have seen enthusiastic treatment of the muscular weakness with potassium precipitate tetany because calcium supplements were not given at the same time.

Anaemia

From the earliest times it has been recognized that steatorrhoea is usually accompanied by anaemia. Gee (1888), in his classical paper, noted "that a fault of sanguification betokened by pallor and a tendency to dropsy is a constant symptom." To-day, largely as a result of the discovery of folic acid and vitamin B_{12}, we know more about the pathogenesis of the anaemia than about any other facet of the syndrome. It is recognized that it may be macrocytic and megaloblastic, iron-deficient, or a combination of both. Indeed, it is the occurrence of macrocytosis with hypochromia in the blood picture which often suggests an intestinal cause for the anaemia when bowel symptoms are minimal. Similarly, in the past, when the multiple nature of the defect was less well understood, treatment with one haematinic might unmask a deficiency of the others, as is shown in Table VIII. The first three patients presented with a macrocytic anaemia, and treatment with folic acid or liver unmasked the iron deficiency; while in the last two the initial hypochromic anaemia became macrocytic after treatment with iron. Occasionally, if the anaemia is severe, immature red and white cells may be seen in the peripheral blood. Leucopenia with a total white-cell count of less than 4,000 per c.mm. occurs in about a third of those with megaloblastic bone-marrow, and sometimes this can lead to troublesome agranulocytic lesions, as in Fig. 3, which shows an agranulocytic ulcer that has perforated right through the lip.

TABLE VIII.—*Change in Blood Picture in Five Patients with Idiopathic Steatorrhoea who were Treated with Folic Acid, Liver, or Iron Alone*

Case No.	Initial Blood Count	Treatment	Time Interval (Months)	Blood Count after Treatment
18	Hb 12·25 C.I. 1·3	Folic acid 20 mg./daily	23	Hb 10·85 C.I. 0·8
45	Hb 12·25 C.I. 1·25 M.C.V. 110 μ^3	Folic acid 10 mg./daily	4	Hb 12·2 C.I. 0·8
44	Hb 10·4 C.I. 1·25	"Liveroid" ½ oz. (15 g.) q.d.s.	29	Hb 14·9 C.I. 0·8
30	Hb 7·0 C.I. 0·65 M.C.V. 82 μ^3	Ferrous sulphate 0·4 g. t.d.s.	5	Hb 11·0 C.I. 1·2
33	Hb 8·3 C.I. 0·66	Ferrous sulphate 0·2 g. t.d.s.	5	Hb 14·2 C.I. 1·3

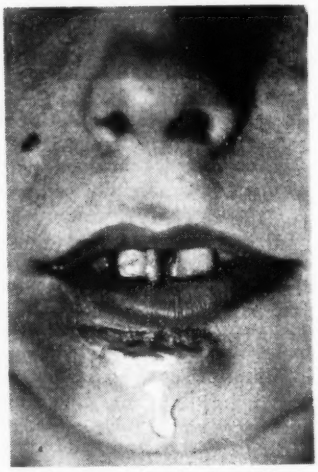

FIG. 3.—Agranulocytic ulcer of lower lip in a patient with steatorrhoea and leucopenia. (Reprinted from *Modern Trends in Gastroenterology*, series I. Butterworth, London.)

Although leucopenia occurs in all forms of megaloblastic anaemia, severe agranulocytic lesions are much more common in the steatorrhoeas where there is a combined deficiency of folic acid and vitamin B_{12} than in Addisonian pernicious anaemia itself.

The basic cause of the anaemia is failure to absorb folic acid, vitamin B_{12}, and iron. Theoretically at least, deficiencies of copper, vitamin C, and pyridoxine may also occur, but there is no evidence that lack of these substances plays a significant part in producing the anaemia.

Soon after it was introduced in 1945, folic acid was shown to be effective not only in the megaloblastic anaemia of tropical sprue and idiopathic steatorrhoea but also when the anaemia occurred in association with gross disease of the bowel (Darby and Jones, 1945; Moore, Bierbaum, Welch, and Wright, 1945; Heyeraas, 1949). Many of these cases had previously proved resistant to all forms of liver extract. The success of folic acid not only in these but also in the group of achrestic anaemias suggests that many of the latter patients may have been suffering from occult steatorrhoea or some other form of intestinal disease.

Initially, folic acid was hailed as the answer to all forms of intestinal megaloblastic anaemia, but we now know that lack of vitamin B_{12} also plays a prominent part in their aetiology.

Absorption of Vitamin B_{12}

In patients with megaloblastic anaemia and the malabsorption syndrome, particularly those cases due to blind loops of bowel or to diverticulosis of the upper intestine, the level of vitamin B_{12} in the serum is often as low as that found in untreated pernicious anaemia (Fig. 4) (Spray, 1960). There are several causes for this deficiency. Castle, Rhoads, Lawson, and Payne (1935), in one of their classical experiments, showed that patients with sprue in relapse are unable to secrete intrinsic factor, but that the secretion returns when the patient enters a remission. However, it is clear that the failure to absorb vitamin B_{12} which occurs in idiopathic steatorrhoea is not due primarily to lack of intrinsic factor.

Fig. 5 shows the percentage of an oral dose of 0.5 μg. of vitamin B_{12} labelled with radioactive cobalt recovered from the faeces of a group of normal persons, of patients with pernicious anaemia, and of seven patients with idiopathic steatorrhoea (Callender and Evans, 1955). The black columns indicate the percentage of the dose found in the faeces when the vitamin was given alone, and the shaded and cross-hatched columns the effect of adding intrinsic factor to the dose of the vitamin. When the vitamin is given alone many of the patients with idiopathic steatorrhoea excrete as much in the faeces as do the patients with pernicious anaemia. When intrinsic factor is added, some of those with steatorrhoea show an improvement in absorption, but the effect is not as dramatic or as consistent as in pernicious anaemia itself. These results suggest that the prime cause of the defect in absorption is not lack of intrinsic factor, but that the vitamin is involved in the general failure of absorption which occurs.

Finally, in some patients, notably those with blind loops of intestine or jejunal diverticulosis, bacterial destruction of the vitamin, or competition for it within the lumen of the gut, may play an important part in producing the deficiency.

Girdwood (1959) has shown *in vitro* that organisms from the gut of patients with a blind loop will take up

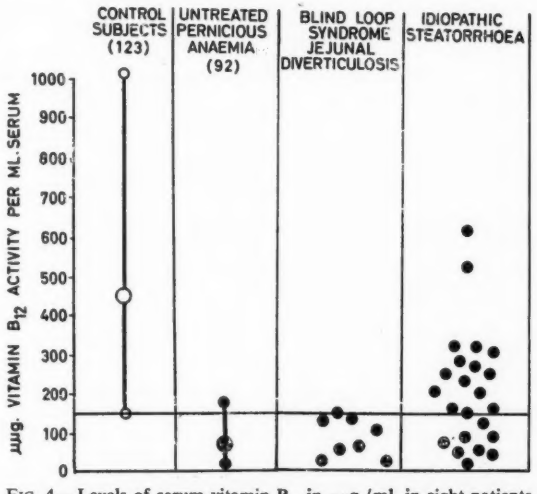

FIG. 4.—Levels of serum vitamin B_{12} in $\mu\mu$g./ml. in eight patients with jejunal diverticulosis and 23 patients with idiopathic steatorrhoea. Mean and range found in a group of control subjects and in untreated patients with pernicious anaemia are shown for comparison. (Data of G. H. Spray.)

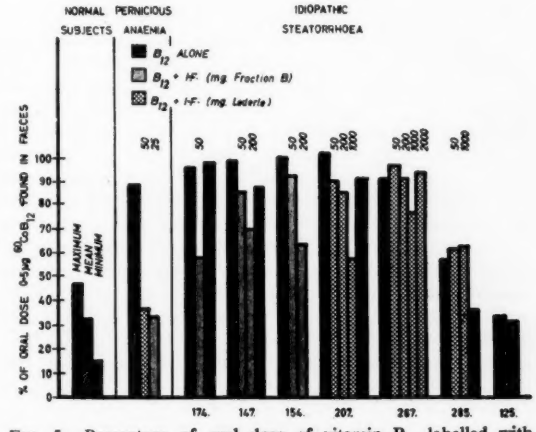

FIG. 5.—Percentage of oral dose of vitamin B_{12} labelled with radioactive cobalt recovered in faeces when given alone and with increasing doses of intrinsic factor. For comparison the excretion in normal subjects is shown and the response in a patient with pernicious anaemia to 25 mg. of Welch Fraction B and to 50 mg. of Lederle intrinsic factor. (Data of S. T. Callender and J. R. Evans, 1955.)

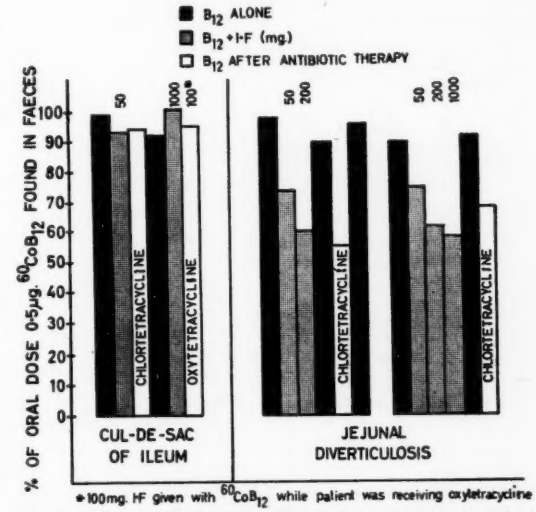

FIG. 6.—Effect of increasing amounts of intrinsic factor and of sterilization of intestine with antibiotics on absorption of oral dose of 0.5 μg. vitamin B_{12} labelled with radioactive cobalt in three patients with megaloblastic anaemia and structural abnormalities of small intestine. Figures above columns are weights in mg. of intrinsic factor preparation given. (Data of J. R. Evans, 1956.)

vitamin B_{12} readily from culture media, and Fig. 6 shows that sterilization of the bowel of these patients with an antibiotic will sometimes improve the absorption of the vitamin without need for other therapy (Evans, 1956). The black columns show the percentage of an oral dose of radioactive vitamin B_{12} recovered from the faeces when the vitamin was given alone to two patients with jejunal diverticulosis, and one with a blind loop. The grey columns show the effect of adding intrinsic factor, and the clear columns the result of treatment with an antibiotic. In both the patients with jejunal diverticulosis the antibiotic improved the absorption of the vitamin. In the patient with the blind loop neither the antibiotics nor the intrinsic factor had any effect, but she was desperately ill and the underlying process had involved most of the bowel (Badenoch, Bedford, and Evans, 1955).

In man, the evidence suggests that folic acid is absorbed mainly from the jejunum while vitamin B_{12} is absorbed from the ileum (Mollin, Booth, and Baker, 1957; Cox, Meynell, Cooke, and Gaddie, 1958); and the fact that in idiopathic steatorrhoea failure to absorb folic acid is almost universal while the absorption of vitamin B_{12} may be normal, suggests that the brunt of the disease falls on the upper small intestine. None the less, clinically the importance of deficiency of vitamin B_{12} cannot be overemphasized. The initial success of folic acid in correcting the megaloblastic anaemia overshadowed the dangers of damage to the central nervous system due to lack of vitamin B_{12}—a danger which is very real, especially in the steatorrhoeas due to anatomical lesions of the bowel where maintenance treatment is unlikely to influence significantly the power of the gut to absorb essential materials.

Iron Deficiency

The deficiency of iron which commonly occurs in idiopathic steatorrhoea is also the result of a failure of absorption. When a dose of 200 mg. of ferrous sulphate labelled with ^{59}Fe is given by mouth to a normal person (Fig. 7) some 5 to 8% appears in the blood, about 85% is recovered from the faeces, and the remainder goes to the body stores and cannot be recovered. If the same dose is given to a patient with simple iron deficiency a very much larger proportion appears in the blood (Badenoch and Callender, 1954a). Fig. 8 shows that, in contrast, in patients with idiopathic steatorrhoea almost all the oral dose is recovered from the faeces and very little appears in the blood, even in the presence of a severe iron-deficiency anaemia. The importance

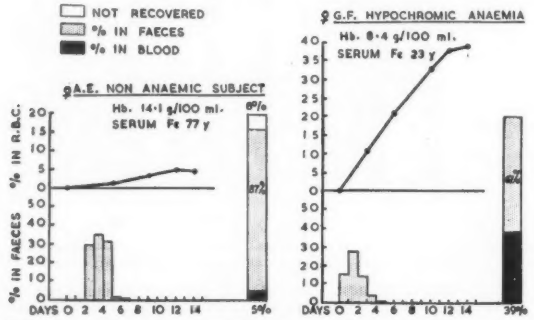

FIG. 7.—Radioactivity appearing in red cells and faeces of normal subject and one with hypochromic anaemia after an oral dose of 200 mg. of ferrous sulphate (5 μc. ^{59}Fe). (Data of J. Badenoch and S. T. Callender, 1954a.)

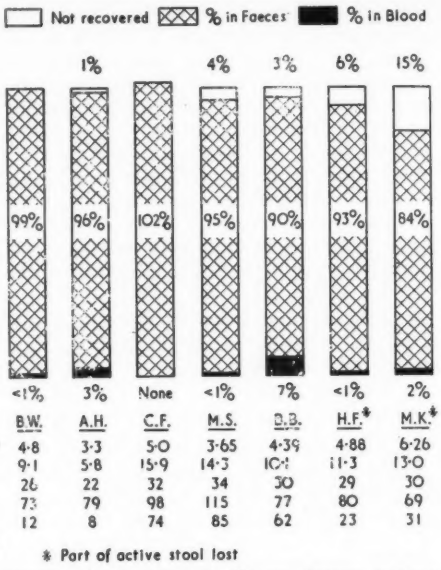

FIG. 8.—Recovery of oral dose of 200 mg. ferrous sulphate labelled with ^{59}Fe in seven patients with steatorrhoea.

of impaired absorption in producing the iron deficiency is emphasized by the response to treatment, for a course of parenteral iron will often restore the haemoglobin rapidly to normal after iron by mouth has failed (Fig. 9).

In some patients with idiopathic steatorrhoea poor absorption may not be the only cause of the iron deficiency, because Dr. Callender and I encountered a few who appeared to absorb enough iron to keep themselves in balance and yet suffered recurrent anaemia (Badenoch and Callender, 1954b). It may be that in these there was intermittent bleeding which we could not detect, but it is also possible that the loss of iron into the intestine from the seepage of serum or from increased desquamation of epithelium may be greater in the presence of steatorrhoea than in normal subjects. In any event, the impaired absorption of iron in idiopathic steatorrhoea and coeliac disease allows nothing for additional demands. I believe that this accounts for the fact that iron deficiency is the common cause of anaemia in the coeliac child, and explains why the symptoms of idiopathic steatorrhoea, in which tiredness and breathlessness are prominent, declare themselves at an earlier age in women than they do in men.

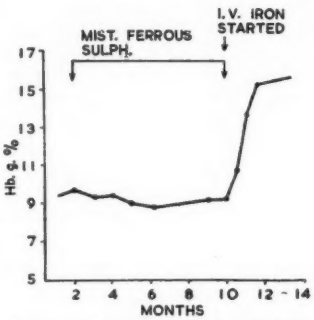

FIG. 9.—Woman, aged 36, with idiopathic steatorrhoea and hypochromic anaemia. Response to treatment with intravenous iron after failure to respond to iron by mouth.

In steatorrhoea due to anatomical disease of the bowel or to pancreatic failure the absorption of iron is usually normal, and when iron-deficiency anaemia occurs it is the result of bleeding.

Obscure Cases

In spite of advances in knowledge, there is still one part of the clinical picture of the malabsorption syndrome which we cannot explain. From time to time we see patients with a peripheral neuropathy, or damage to the central nervous system, which resist all our efforts to relieve them. There were four in my series, suffering respectively from idiopathic steatorrhoea, tabes mesenterica, Whipple's disease, and diverticulosis of the small intestine. The first three had progressive glove-and-stocking anaesthesia, with loss of reflexes, and the fourth had a myeloradiculopathy involving the cord. In two the C.S.F. was normal, in the other two the level of protein was raised, but there were no other abnormalities.

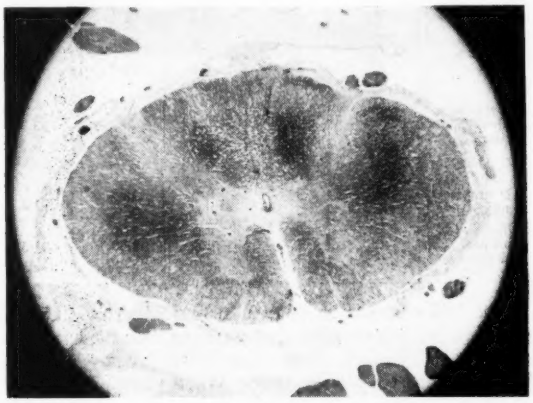

FIG. 10.—Section of lumbar spinal cord (stained for myelin) of patient with steatorrhoea and a myeloradiculopathy, showing generalized demyelination with some sparing of lateral columns.

Fig. 10 shows a section of the lumbar cord, stained for myelin, of the patient with the myeloradiculopathy. The black areas in the region of the pyramidal tracts are the only areas unaffected by the generalized demyelination which is maximal in the posterior columns. The curious thing about this syndrome is that it can occur while the patient is in haematological remission and in fair health, and it is totally uninfluenced by massive doses of all the known vitamins and minerals. It is tempting to assume that it is due to lack of an essential factor, but this is pure hypothesis. Its origin is entirely obscure and it presents a challenge for the future.

Fatal Cases

Before I leave the clinical part of my story, and lest I give the impression that, apart from a stubborn neurological syndrome, medical science has triumphed, it will be as well to remind ourselves that steatorrhoea is still a dangerous disease. In my series of 163, there have been 21 deaths, almost 13%. It is true that this study extends over a number of years, and to-day we would have saved some of these patients, but four of them died in 1959, in spite of our best efforts. Of the 21 deaths, nine occurred in the idiopathic group and 12 among the remainder.

To take first the 12 in which the steatorrhoea was symptomatic of a wider pathological process (Table IX). Three had cancer and a fourth developed massive gangrene of the bowel after mesenteric thrombosis.

TABLE IX.—*Causes of Death in the 12 Patients in Whom Steatorrhoea was Secondary to a Wider Pathological Process*

Case	Diagnosis	Cause of Death
K.F., C.J.	Carcinoma of pancreas	Carcinomatosis
L.M.	,, caecum-resection	Pneumonia
R.B.	Mesenteric thrombosis	Gangrene of bowel
E.B., J.M.	Diverticulosis of jejunum	Pneumonia
I.R.	,,	Myelopathy
D.B., J.S.	Tabes mesenterica	Pneumonia, Volvulus
V.R.	Crohn's disease	Perforated duodenal ulcer, steroids
M.S.	,,	Cachexia
B.F.	Whipple's ,,	,, neuropathy

Among the eight remaining patients it is interesting to note that three suffered from progressive neurological disease, and one of these died of acute intestinal obstruction as a result of volvulus. Three of the eight patients with upper intestinal diverticulosis have died, not, I think, because it is a particularly dangerous syndrome, but because it occurs chiefly among the elderly whose days are numbered for other reasons. One of the patients with Crohn's disease, a woman, died of a perforation of a duodenal ulcer while receiving steroids.

TABLE X.—*Causes of Death in Nine Patients with Idiopathic Steatorrhoea*

Case	
M.W.	Oesophageal stricture-perforation
W.P.	Bronchopneumonia
L.F.	Pneumonia, Steroids
D.C., K.W.	Muscular weakness ? Hypokalaemia
G.E., S.P.	Hepatic failure
J.T.	Volvulus—acute obstruction
W.B.	Cachexia, neuropathy

Of the nine deaths in the idiopathic group (Table X), in only two, M.W. and W.P., could the deaths be said to be unrelated to the malabsorption syndrome. In one of these, M.W., attempts to dilate an oesophageal stricture led to a fatal mediastinitis; and W.P. was an old man who succumbed to bronchopneumonia.

L.F. was one of the first patients whom I treated with cortisone. She died of an uncontrollable respiratory infection which seemed to be related to its use. D.C. and K.W. suffered progressive muscular weakness and, in retrospect, almost certainly succumbed to potassium deficiency. G.E. and S.P. died in hepatic coma, and illustrate the point that the combination of liver disease and steatorrhoea is a lethal one. S.P. was all the more unfortunate because he was one of the two with massive retroperitoneal haemorrhage described earlier, and we had good reason to suppose that his hepatitis was due to homologous serum jaundice, resulting from the blood transfusions which he had received. Once again intestinal obstruction appears in the list. W.B. died in our wards last year of progressive inanition, in spite of full replacements of vitamins and minerals, a gluten-free diet, and treatment with steroids. Necropsy failed to reveal a malignant cause for his steatorrhoea, and we are forced to admit that we have no idea why he died. His death emphasized more strongly to me than anything else has done that for all our efforts, and in spite of much greater understanding of some facets of the problem, the basic defect in idiopathic steatorrhoea still remains unknown.

[*The second lecture, together with a list of references, will appear in our next issue.*]

ABSORPTION AND ELIMINATION OF ^{15}N AFTER ADMINISTRATION OF ISOTOPICALLY LABELLED YEAST PROTEIN AND YEAST PROTEIN HYDROLYSATE TO ADULT PATIENTS WITH COELIAC DISEASE

II. ELIMINATION OF ISOTOPE IN THE URINE AND FAECES

BY

C. W. CRANE,* M.B., B.Sc., A.R.I.C.

AND

A. NEUBERGER, M.D., Ph.D., F.R.S.

The Department of Chemical Pathology, St. Mary's Hospital Medical School, London

Digestion in the normal human subject and the abnormalities in the enzymic hydrolysis and absorption of protein which are found in adult coeliac disease, as shown by investigations using ^{15}N-labelled protein and protein hydrolysate, were discussed in two previous papers (Crane and Neuberger, 1960a, 1960b). This communication is concerned with the excretion of isotopic nitrogen in the urine, the origin of faecal nitrogen in normal man and in certain cases of steatorrhoea, and the possible effects on the general nutrition of the patient of increased nitrogen excretion in the faeces. Analyses of urine and faeces were carried out on the four patients investigated in the first paper of this series (Crane and Neuberger, 1960b), but we include the results of another patient who suffered from adult coeliac disease and who excreted an unusually large amount of nitrogen in his faeces. To this patient ^{15}N-labelled glycine was administered and the effect on faecal nitrogen of varying the protein intake of the diet was examined.

RESULTS

Excretion of ^{15}N in the Urine

In three experiments, A_2, C_2, and J_1 (Table I), in which normal subjects were fed yeast protein equivalent to about 0.9 mg. of ^{15}N/kg. body weight, and allowed diets of their own choosing, the total ^{15}N eliminated in the urine during the subsequent three days was remarkably constant. Values expressed as percentages of the amounts of ^{15}N fed were 26.3, 26.6, and 27.4%. When labelled yeast protein hydrolysate was fed, equivalent to 0.83 mg. ^{15}N/kg. body weight in a similar experiment (C_3), the excretion was 28.1%, but in a second experiment (A_3) only 23.5% of the ^{15}N was excreted in the urine in three days. However, this subject fasted overnight and for the first 12 hours of the experiment, and 250 ml. of blood was withdrawn; hence it is possible that this lower value reflects some degree of nitrogen retention. Excretion was higher when labelled yeast protein was fed to two subjects placed on measured diets, adequate in protein but deficient in calories, and values for three-day periods were 30.0 and 31.9% of the ^{15}N fed (experiments A_1 and C_1).

Compared with the findings in normal subjects, the ^{15}N excreted in the urine after three days was much more variable when either whole-yeast protein or protein hydrolysate was fed to patients with coeliac disease. Table I shows the results of seven of these experiments. After receiving protein three patients (experiments W_1, K_1, and H_1) excreted 9, 32, and 43% respectively less ^{15}N in the urine at the end of three days than did normal subjects on the average. The tendency of patients with coeliac disease to excrete only a relatively small proportion of the administered ^{15}N in the urine is also apparent in two out of three hydrolysate experiments shown in Table I.

TABLE I.—*Elimination of ^{15}N in Urine and Faeces During Three Days After Feeding Labelled Yeast Protein and Protein Hydrolysate (Equivalent to 0.4–0.9 mg. ^{15}N/kg. Body Weight) to Normal Subjects and Patients with Adult Coeliac Disease. Values are Expressed as Percentages of the ^{15}N Administered*

	Experiment	Urine	Faeces	Total	Average
		Protein			
Normal subjects	A_1	30·0	5·4	35·4	33·1
	A_2	26·3	6·3	32·6	
	C_1	31·9	3·6	35·5	
	C_2	26·6	—	—	
	J_1	27·4	1·5	28·9	
	WK	—	6·7	—	
Patients with adult coeliac disease	G_1	32·2	11·2	43·4	33·3
	W_1	24·4	9·2	33·6	
	K_1	18·1	12·4	30·5	
	H_1	15·2	10·2	25·4	
		Hydrolysate			
Normal subjects	A_3	23·5	4·7	28·2	31·1
	C_3	28·1	6·0	34·1	
Patients with adult coeliac disease	W_2	28·3	8·6	36·9	31·6
	H_2	17·2	11·8	29·0	
	G_2	20·4	8·6	29·0	

The ^{15}N elimination in two further experiments with a coeliac patient suggests that nitrogen metabolism in its quantitative aspects may vary considerably over a relatively short period of time. When yeast protein was given in experiment G_1 (Table I), the ^{15}N excreted was about 12% higher than normal—that is, 32.2% of the amount fed—but when the hydrolysate was substituted 12 days later (experiment G_2), the amount of ^{15}N was diminished, being about 70% of that excreted by the normal subject.

Excretion of ^{15}N in the Faeces of Normal Subjects

Compared with the excretion of ^{15}N in the urine after feeding labelled yeast protein to normal subjects, the amount of ^{15}N eliminated in the faeces at the end of three-day periods was much more variable. In four experiments, A_1, A_2, C_1, and WK (Table I), when protein was fed equivalent to 0.4–0.9 mg. ^{15}N/kg. body weight, values were 5.4, 6.3, 3.6, and 6.7% of the amount fed. In two of these experiments where stool collections were continued up to six days, a further 1% only of the isotope was excreted. Fig. 1 and Table II show the results in detail of two of these experiments. The bulk of the ^{15}N was eliminated during the first 48 hours after feeding and the maximum isotope concentration appeared during this time. In three out of six experiments in which yeast protein or hydrolysate were fed to normal subjects, the maximum output of labelled nitrogen in the faeces occurred in the first 24 hours, while in the other three experiments the maximum output of the isotope was in the second 24-hour period. After the first 48 hours the proportion of ^{15}N eliminated in the faeces diminished rapidly and fell to a value between 0.1 and 0.2% of the dose on the sixth day, the isotope content remaining at 0.006 atoms% excess after the third day.

Fig. 1 and Table II also show the amounts of faecal nitrogen soluble in 5% trichloroacetic acid (T.C.A.) and

*Now at the Department of Medicine, Queen Elizabeth Hospital, Birmingham, 15.

the percentage of T.C.A.-soluble ^{15}N. In three experiments about one-third of the total nitrogen and of the ^{15}N were in this form, and thus the ^{15}N content of the T.C.A.-soluble nitrogen (Table II) was similar throughout to that of the total faecal nitrogen. In another experiment (J_1) only 3.5% of the total ^{15}N fed appeared in the faeces after six days. During the first two days the total nitrogen excreted was 1.5

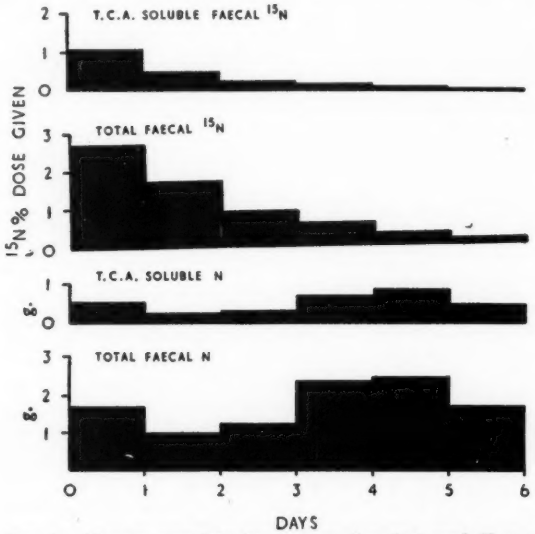

FIG. 1.—After an overnight fast, a normal patient aged 42 was given 75.3 mg. of ^{15}N in the form of yeast protein (experiment A_1). Faeces were collected for six days and a normal diet was allowed throughout the period.

TABLE II.—*A Normal Subject, W. K., Aged 62, was Given, After Fasting Overnight, Yeast Protein Containing 30.5 mg. of ^{15}N (0.41 mg. ^{15}N/kg. body weight) in 250 ml. of Water. He Was Allowed a Normal Diet, and Faeces Were Collected for Six Days*

Time (Days)	Total Nitrogen			T.C.A.-soluble Nitrogen		
	N (mg.) a	^{15}N Atoms % Excess b	% ^{15}N given Eliminated/Day $\frac{a \times b}{30.5}$	N (mg.) c	^{15}N Atoms % Excess d	% ^{15}N given Eliminated/Day $\frac{c \times d}{30.5}$
1	1,980	0·030	1·93	650	0·036	0·77
2	3,330	0·041	4·50	1,200	0·038	1·50
3	1,350	0·006	0·28	490	0·008	0·13
			6·71			2·40
4	2,180	0·006	0·45	898	0·005	0·16
5	1,605	0·006	0·34	732	0·006	0·15
6	1,082	0·006	0·22	450	0·006	0·09
		Total	7·72		Total	2·80

and 2.2 g., but the ^{15}N contents were only 0.004 and 0.002 atoms% excess and the percentages of isotope excreted only 0.1% and 0.08% of the amounts fed. The maximum ^{15}N content did not appear until the fifth day. Although the isotope contents of the T.C.A.-soluble nitrogen and total nitrogen were similar, a smaller percentage (20%) of the nitrogen was soluble in T.C.A.

We must comment briefly on the significance of the low ^{15}N value obtained in faecal specimens in some of the experiments reported here (Tables II–VI). The reproducibility of the figures for atoms% ^{15}N with the mass spectrometer used and the range of values under consideration is about $\pm$ 0.002 to $\pm$ 0.003 atoms% excess. It has been suggested (Sharp *et al.*, 1956) that the nitrogen obtained from biological material may be enriched with respect to ^{15}N up to about 0.006 atoms% excess if compared with gaseous nitrogen obtained from a commercial source. Our blank values were obtained with analytically pure ammonium sulphate which was found by Sharp *et al.* to have on the average 0.0048% more ^{15}N than the commercial gaseous nitrogen. We have therefore assumed that values for ^{15}N of 0.004% or less are probably not significant, but that figures lying between 0.005 and 0.015 are significant but may be in error by a considerable amount, depending on the abundance of ^{15}N found.

After feeding the enzymic hydrolysate to two normal subjects, the amounts of ^{15}N excreted after three days were 4.7 and 6.0% (experiments A_3 and C_3, Table I) of the amounts fed, and Table III gives the results in detail

TABLE III.—*Labelled Yeast Protein Hydrolysate, Containing 50.4 mg. of ^{15}N and Equivalent to 0.6 mg. ^{15}N/kg. was Given to a Normal Male Subject Weighing 83 kg. After Fasting for 10 Hours (Experiment A_3). A Normal Diet was Given*

Time (Days)	Total Nitrogen			T.C.A.-soluble Nitrogen		
	N (mg.) a	^{15}N Atoms % Excess b	% ^{15}N given Eliminated/Day $\frac{a \times b}{50.4}$	N (mg.) c	^{15}N Atoms % Excess d	% ^{15}N given Eliminated/Day $\frac{c \times d}{50.4}$
1	2,540	0·035	1·77	650	0·054	0·69
2	2,000	0·059	2·33	525	0·083	0·87
3	980	0·032	0·6	334	0·038	0·25
			4·70			1·81

of one of these experiments. As in the previous studies with whole-yeast protein, the bulk of the ^{15}N was eliminated in the first two days. A most significant finding from these two experiments was that the proportions of T.C.A.-soluble nitrogen and T.C.A.-soluble ^{15}N were, as for the protein experiments, about one-third of the total nitrogen and ^{15}N excreted. Thus it appears that the isotope is incorporated and eliminated to a very large extent as faecal protein, irrespective of whether insoluble whole-yeast protein or water-soluble protein hydrolysate consisting mainly of amino-acids is fed.

Excretion of ^{15}N in Faeces of Adult Patients with Coeliac Disease

As can be seen from Table I of the first paper of this series (Crane and Neuberger, 1960b) the average values for the daily nitrogen excretion in the faeces in all four patients were in excess of normal figures, such as those given by Cooke *et al.* (1953), but day-to-day variations in the same patient were considerable (Tables IV *et seq.*).

TABLE IV.—*23.6 mg. of ^{15}N in the Form of Yeast Protein (0.4 mg./kg. Body Weight) was Given to a Patient Aged 67 Years With Adult Coeliac Disease, After Fasting Overnight (Experiment H.). Faeces were Collected for Six Days, and a Normal Ward Diet was Allowed throughout this Period*

Time (Days)	Total Nitrogen			T.C.A.-soluble Nitrogen		
	Total N (mg.) a	^{15}N Atoms % Excess b	% ^{15}N given Eliminated/Day $\frac{a \times b}{23.6}$	Total N (mg). c	^{15}N Atoms % Excess d	% ^{15}N given Eliminated/Day $\frac{c \times d}{23.6}$
1	3,480	0·030	4·35	1,300	0·036	2·00
2	3,140	0·032	4·30	1,090	0·033	1·50
3	1,770	0·020	1·50	1,040	0·019	0·85
			10·15			4·35
4	4,730	0·013	2·50	1,750	0·012	0·90
5	1,760	0·009	0·70	691	0·009	0·27
6	3,900	0·009	1·50	1,450	0·009	0·56
		Total	14·85		Total	6·08

When labelled yeast protein equivalent to 0.4 mg. ^{15}N/kg. body weight was fed to patients with adult coeliac disease, the amounts of isotope eliminated at the end of three- and six-day periods as percentages of the amounts given were much greater than for normal subjects (Table I). Table IV gives the results of one of these experiments. The percentage of ^{15}N excreted in three days was 10.2, and in three further experiments, W_1, G_1, and K_1 (Table I), values were 9.2, 11.2, and 12.4. In the experiment outlined in Table IV and in two other experiments, the stools were collected and analysed for a further three days, during which time a further 4.8, 2.4, and 9.4% of the administered dose were eliminated. As in the previous experiments, the bulk of the isotope appeared in the faeces collected during the first two days, but Table IV and Fig. 2 emphasize that the quantity of isotope excreted after the third day of each experiment was considerable, and this is in marked contrast to the findings in most normal subjects. The ^{15}N contents were, however, slightly higher than those obtained in the experiments with normal subjects, but the proportions of T.C.A.-soluble nitrogen and ^{15}N were each about one-third respectively of the total nitrogen and ^{15}N excreted in two experiments, and thus the same as in the previous experiments with normals. In general, the pattern of the nitrogen excretion, and hence the ^{15}N, followed that of the fat, and this is shown in Fig. 2.

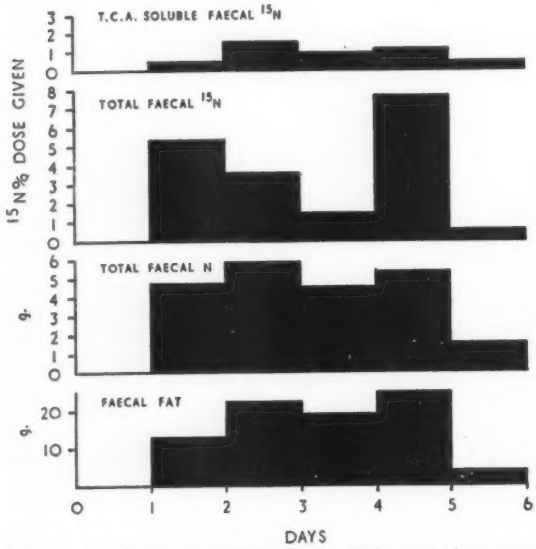

FIG. 2.—A patient aged 61 and weighing 56 kg. was given yeast protein equivalent to 0.4 mg. of ^{15}N/kg. body weight (experiment W_1). Faeces were collected on the following six days and during this time a normal ward diet was allowed. No faeces were passed during the first day of this experiment.

When the protein hydrolysate was fed to three patients in the same proportion of ^{15}N to body weight, the quantity of ^{15}N excreted in the faeces in the first three-day period was about the same as when the whole protein was given. Values were 8.6, 8.6, and 11.8% of the quantities fed (experiments W_2, G_2, and H_2), and, as in the previous experiments, the bulk of the isotope was eliminated during the first two days. In one experiment a further 4.9% was excreted when the collection was prolonged to six days, and details are given in Table V. In this experiment the proportions of T.C.A.-soluble nitrogen to total nitrogen and T.C.A.-soluble ^{15}N to total ^{15}N were slightly higher than in the previous experiments, and were about 40%. These slightly higher proportions were also found in a second experiment where faecal collections were made for three days only.

TABLE V.—*26 mg. of ^{15}N was Given in the Form of Yeast Protein Hydrolysate to a Patient, H. G., Who was Suffering from Coeliac Disease. Faeces were Collected for Six Days and a Normal Diet was Allowed*

Time (Days)	Total Nitrogen			T.C.A.-soluble Nitrogen		
	Total N (mg.) a	^{15}N Atoms % Excess b	% ^{15}N given Eliminated/ Day $\frac{a \times b}{26}$	Total N (mg.) c	^{15}N Atoms % Excess d	% ^{15}N given Eliminated/ Day $\frac{c \times d}{26}$
1	6,350	0·031	7·60	2,580	0·046	4·50
2	3,660	0·025	3·40	1,045	0·030	1·20
3	1,039	0·020	0·80	356	0·018	0·25
			11·80			5·95
4	5,280	0·012	2·40	2,000	0·010	0·73
5	5,710	0·010	2·10	2,080	0·006	0·48
6	1,145	0·010	0·40	498	0·006	0·11
		Total	16·70		Total	7·27

These results show that patients with coeliac disease excrete in the faeces a much larger proportion of the administered ^{15}N compared with normal subjects, and the figures are similar when either the whole-yeast protein or the protein hydrolysate is fed. Moreover, in the four experiments where the stools were analysed for T.C.A.-soluble nitrogen it was found that, irrespective of the type of material fed, 60% or more of the isotope was found to be eliminated in a form insoluble in T.C.A.

Table I also shows that the total amount of ^{15}N eliminated, expressed as a percentage of the ^{15}N of labelled protein or hydrolysate administered, is more or less the same in patients with steatorrhoea and in normal persons. But the latter excrete during the three days after the administration of the labelled material four to ten times as much of the ^{15}N in the urine as in the faeces; in coeliac patients the ratio varies between 1.5 and 3.5.

Excretion of Isotope from Feeding ^{15}N-labelled Protein to a Coeliac Patient in Remission After a Gluten-free Diet

In Part I of this investigation the absorption of ^{15}N-labelled yeast protein was found to be normal in a patient, B. K., who made a rapid clinical improvement 14 days after recommencing a gluten-free diet. She had abandoned the diet some months prior to admission, in consequence of which the fatty diarrhoea returned; there was rapid loss of weight, hypoalbuminaemia, and

TABLE VI.—*In Both Experiments Patient B. K. Received 18 mg. of ^{15}N in the Form of Isotopically Labelled Yeast Protein After an Overnight Fast. Further Details are Given in the Text*

Day	Total Fat (g.)	Total N (g.) a	^{15}N Atoms % Excess b	% ^{15}N given Eliminated Day $\frac{a \times b}{18{\cdot}00}$
		A. Findings during Remission		
1	0	0	0	0
2	11·2	2·15	0·016	1·90
3	7·3	1·31	0·006	0·40
4	13·6	2·46	0·033	4·50
				6·80
		B. Findings during Relapse		
1	3·7	1·24	0·077	1·15
2	28·0	4·52	0·039	9·70
3	13·8	2·04	0·013	1·47
				12·32

peripheral oedema. Stools were collected for four days after the patient took the labelled yeast protein since she was constipated during the first day, but up to this time she had her bowels open once or twice a day. The results of the faecal analyses from the experiment are set out in Table VI A, and the findings from a similar experiment carried out some eight months previously, when the patient was in relapse and was taking a normal diet, are set out in Table VI B. Protein was supplied equivalent to 0.4 mg. ^{15}N/kg. body weight. It appears that over these short periods of time there was but slight reduction in the quantities of fat and nitrogen excreted when the patient was put on to a gluten-free diet, but the ^{15}N contents of the nitrogen were lowered during the gluten-free period, and thus the quantity of isotope eliminated was less and within the limits found for normal subjects.

Results Obtained on Administering Diets of Varying Nitrogen Content and ^{15}N Glycine to a Patient Suffering from Coeliac Disease

We wish to record the results of an earlier investigation of a patient with coeliac disease who had an abnormally high excretion of nitrogen in the faeces.

Case History

R., a man aged 45, a presumptive coeliac in childhood, had a sudden attack of diarrhoea with bulky fatty stools in 1940, when 30 years old and while serving in the Army. The diarrhoea occurred about once a year until 1951, when he was admitted to hospital with a myocardial infarct, after which the diarrhoea became persistent and was followed by severe loss of weight, ankle oedema, glossitis, anaemia, and tetany.

From 1952 until his final admission in 1955 he was treated in hospital on several occasions with folic acid, vitamins, and low-fat and gluten-free diet, but relapses were frequent. On admission in December, 1955, he was wasted, pale, apathetic, with a large protuberant abdomen. His fingers were clubbed and his tongue was smooth. His blood-pressure was 105/60, and there was oedema of the legs and ascites. A barium-meal examination showed loss of normal pattern of the small intestine, and faecal fat was 30% by weight of a dried 24-hour specimen. The haemoglobin was 65%, serum proteins 3.8 g./100 ml. (albumin 1.0 g./100 ml.), and serum calcium was 8.3 mg./100 ml. On duodenal intubation and stimulation of pancreatic secretion with secretin, aspirated juice gave normal values for diastase and lipase, and values near the lower limit of normal for trypsin. He improved slightly on reinstituting the gluten-free regime and cortisone, and, later, attempts were made to improve his nutrition with high-protein feeding (see below).

After a period of steady deterioration his diarrhoea suddenly became very much worse and was accompanied by a swinging temperature and severe abdominal pain; later there was marked abdominal distension. He became electrolyte-depleted, with plasma Na^+ 121 and Cl^- 82 mEq/l., and 24 hours before death his blood-pressure fell to 75/40.

Post-mortem examination showed severe atheroma, narrowing of the anterior descending branch of the left coronary artery, and ulcerated plaques in the abdominal aorta. There were pleural adhesions at the right apex of the lung, with some tuberculous cavitation, and at the left base an area of tuberculous bronchopneumonia. The pleural cavity contained a quantity of turbid exudate. The small intestine was grossly distended and contained altered blood, and there were a number of shallow ulcers scattered throughout the small gut. The pancreas was normal.

Nitrogen Balance and Faecal Nitrogen.—As Table VII shows, during a six-day period, when the daily calculated dietary intake of nitrogen was 12.5 g. (supplied as normal food), the patient was in negative nitrogen balance to the extent of 4 g./day and his average daily faecal nitrogen excretion amounted to 5.6 g., which was equivalent to 34% of the total nitrogen excreted. When the nitrogen intake was increased to 28 g./day his output also increased, but the nitrogen balance improved and, allowing for analytical errors, approached zero. However, the proportion of nitrogen excreted in the faeces increased to between 42 and 43% of the total output, and during the six-day period the average faecal nitrogen excretion was 12.6 g.; this is approximately the urinary nitrogen output of a normal subject. During the third six-day period the patient was given a diet consisting of 26 g. of protein and 59 g. of protein hydrolysate (as "nesmeida"), making a total daily nitrogen intake of 11 g. During this period the patient excreted in his faeces an average of 30% of the total nitrogen eliminated from the body, and the nitrogen balance became negative but not so markedly as during the first feeding period.

TABLE VII.—*Patient R, With Adult Coeliac Disease, Received Protein Equivalent to 78 and 175 g./day for Two Periods of Six Days, During Which Time all Urine and Faeces were Collected. A Three-day Equilibrium Period was Allowed in Each Experiment. A Further Experiment was Carried Out in Which the Nitrogen was Supplied as 26 g. of Protein and 59 g. of Protein Hydrolysate*

Period (3 Days)	N Intake (g./Day)	Average Daily N Output (g./Day)			Balance (g. N/Day)
		Urine	Faeces	Total	
78 g. of Protein Fed Daily					
1	12·5	11·3	5·6	16·9	−4·4
2	12·5	10·5	5·6	16·1	−3·6
175 g. of Protein Fed Daily					
1	28·0	16·1	12·6	28·7	−0·7
2	28·0	16·8	12·6	29·4	−1·4
26 g. of Protein and 59 g. of Hydrolysate Fed Daily					
1	11·0	9·3	4·1	13·4	−2·4
2	11·0	9·5	4·1	13·6	−2·6

Administration of ^{15}N Glycine.—The patient was given 475 mg. of ^{15}N-labelled glycine containing 31.44 atoms% excess ^{15}N immediately before breakfast and after an overnight fast. Urine was collected for 48 hours and faeces for three days, and a diet of his own choosing was allowed throughout this period. The isotope contents of the total nitrogen, urea, and ammonia in the urine were measured by methods already referred to. The results are not given in detail, but the following points may be mentioned. The patient excreted in the urine during the first 48 hours 26.7% of the total isotope administered, and the maximum ^{15}N concentration was found in the urea during the second three-hour period (three to six hours) after administration, and was 0.080 atoms% excess, while the isotope concentration of the ammonia was higher in the first three-hour period and was 0.121 atoms% excess. The isotope results relating to the faeces are given in Table VIII. The ^{15}N concentrations found in the faeces were lower than those found later in experiments when labelled protein was fed. For reasons which have been mentioned above, values for ^{15}N less than 0.004 atoms% excess are of doubtful value; the figures given in Table VIII are between two and four times this value,

TABLE VIII.—*475 mg. of Labelled Glycine (0.6 mg. ^{15}N/kg.) was Given to a Fasting Coeliac Patient, Who had Breakfast Immediately Afterwards. The Patient was Allowed a Normal Ward Diet, and Faeces were Collected for Three Days*

Time (Days)	Total Faecal Nitrogen			T.C.A.-soluble Faecal Nitrogen		
	Total N (mg.) a	^{15}N Atoms % Excess b	% ^{15}N given Eliminated/ Day $\frac{a \times b}{28 \cdot 4}$	Total N (mg.) c	^{15}N Atoms % Excess d	% ^{15}N given Eliminated/ Day $\frac{c \times d}{28 \cdot 4}$
1	2,680	0·008	0·75	700	0·011	0·27
2	3,680	0·015	1·94	1,190	0·011	0·46
3	8,640	0·013	3·96	2,380	0·015	1·26
			6·65			1·99

but the accuracy is not very high. However, it is concluded that some labelled nitrogen was excreted in the faeces.

Again we found, as in the protein experiments described above, that the ^{15}N content of the T.C.A.-soluble fraction of the faeces was approximately the same as that of the total nitrogen of the faeces. As the total proportion of the T.C.A.-insoluble protein was again about two-thirds of the total faecal nitrogen, it would appear that two-thirds of the labelled nitrogen which was ingested in the form of free glycine was incorporated into more complex structures, probably protein.

DISCUSSION

Origin of Faecal Nitrogen in Normal Man

Daily faecal nitrogen values in normal man on diets consumed in western countries are reported to average between 1 and 2 g./day (Cooke *et al.*, 1953; Wollaeger *et al.*, 1947), but the amount eliminated varies to a large extent with the diet (Lusk, 1928). A large part of this nitrogen must be derived from sources other than the diet. This follows from the fact that on prolonged starvation or complete deprivation of dietary protein, faecal nitrogen is never reduced to zero, and values varying between 0.1 and 0.8 g./day have been reported under such conditions (Mendel and Fine, 1912; Lusk, 1928). F. Voit (1892) and C. Voit (1894) were probably the first to suggest that the bulk of the faecal nitrogen was derived from endogenous sources on the basis of starvation experiments in dogs and also of investigations using a closed isolated loop of the intestine. The suggestion that large amounts of protein, calculated to be equivalent to about one-third of the dietary daily nitrogen intake, are excreted into the small intestine was made by Mosenthal (1911), who used dogs prepared with Thiery–Vella fistulae.

More recent work allows us to be more specific about the origin of faecal nitrogen. There are no reliable quantitative figures available of the amounts of protein which enter the alimentary canal every day in the form of saliva, gastric juice, pancreatic secretion, and succus entericus. Reference has already been made to the calculations of Mosenthal about the protein production of the gut wall, and the work of Borgström *et al.* (1957) has indicated surprisingly high concentrations of trypsin, chymotrypsin, and amylase in the small intestine. In addition, desquamation of the epithelial cells of the villi occurs at a rapid rate (Leblond and Stevens, 1948; McMinn, 1954), and in the species investigated these cells are renewed on the average every one and a half days. It has also been found (Walser and Bodenlos, 1959) that a considerable amount of urea, equivalent to at least 25% of that synthesized per day, is excreted into the gut. Amino-acids may also pass back into the lumen of the intestine, but, so far as we know, this has not been demonstrated.

Cope and Goadby (1935) suggested that in some cases of hypoalbuminaemia without demonstrable causes there may be an increased rate of destruction of albumin. Quantitative studies on the metabolism of plasma proteins in idiopathic hypoproteinaemia were later carried out by Albright *et al.* (1950) and by Schwartz and Thomsen (1957), the latter using ^{131}I-labelled albumin. Hypoalbuminaemia appears to be associated in some cases with a "hypertrophic" gastritis (Citrin *et al.*, 1957), and Gordon (1959), using ^{131}I-labelled polyvinyl-pyrrolidone, produced strong suggestive evidence that the increased loss of albumin was caused by extensive leakage of the protein into the gut. It is still uncertain whether this represents an exaggeration of a normal process, but Holman *et al.* (1959) demonstrated by an immunological technique (Ouchterlony) the presence of albumin and γ-globulin in the intestinal contents of normal persons. It is thus possible that, as suggested by Holman *et al.*, digestion by intestinal enzymes is a mechanism of plasma protein katabolism in the normal subject.

Nasset (for review, see Nasset, 1957) has carried out extensive investigations on digestion in animals, and concluded that the nitrogen content of the chyme is largely independent of dietary protein intake. Although his quantitative data have been criticized by Geiger *et al.* (1958), the general thesis that nitrogenous compounds in the intestine represent a mixture of endogenous and dietary protein is well established. It seems likely that the amount of nitrogen in the form of protein or compounds of low molecular weight delivered into the lumen of the gut is equal to or even greater than that represented by the dietary intake. The two components blend, and in the normal subject about 95% of the total nitrogenous material is hydrolysed and absorbed or reabsorbed by the mucosa.

The results obtained in the present work are in accordance with this concept. In almost all our normal subjects receiving ^{15}N-labelled protein, very little of the label was excreted in the faeces after the third day. If the faecal nitrogen were derived exclusively from dietary protein and originated to an equal extent from all nitrogenous substances of the food, we should be able to predict the average isotope concentration of the faecal nitrogen by dividing the amount of ^{15}N given by the total nitrogen ingested over the period in question. For example, in one experiment a normal subject was given 75 mg. of ^{15}N (isotope excess), and during the next three days the total nitrogen intake was 47 g. The expected average isotope content in the faecal nitrogen is thus 0.157 atoms% excess. The total faecal nitrogen over this period was 3.8 g. and the total ^{15}N excreted in the stools was 4.02 mg. (^{15}N excess). The average observed isotope content was therefore 0.106 atoms% excess—that is, about 65% of the expected value. Calculations for three-day periods in two similar experiments were 0.180% (calculated), 0.094% (observed), and 0.145% (calculated) and 0.079% (observed). When similar calculations were made for shorter or longer periods than three days, the differences between observed and calculated values were much greater. While these calculations are somewhat crude, it is nevertheless, we believe, permissible to conclude that a source other than the diet makes a large contribution to the faecal nitrogen.

Similar results were obtained in experiments where protein hydrolysate was given to two normal subjects. Thus in one experiment 63.6 mg. of ^{15}N (atoms excess) was given to a subject with a nitrogen intake of 14 g./day. The faecal excretion of total nitrogen in the following three-day period amounted to 5.22 g. and the ^{15}N to 4.1 mg. The calculated value on the basis of the assumptions stated above was 0.163 atoms% excess, while the observed value was 0.078—a difference similar to those observed for whole protein. If incomplete hydrolysis of ingested whole protein had been mainly responsible for the faecal nitrogen one would have expected that administration of ^{15}N in the form of soluble amino-acids would result in a much lower labelling of the faecal nitrogen. It is therefore assumed that, in addition to the contribution made by dietary nitrogen, part of the labelling of faecal nitrogen is the result of the sequence of processes consisting of absorption of labelled

amino-acids and peptides by the mucosa, the participation of those substances in anabolic and katabolic processes within the body, followed by secretion or elimination of urea or proteins and other substances into the gut, as discussed above.

Further support for the concept that faecal nitrogen is derived both from endogenous and from exogenous sources comes from the demonstration that the concentrations of ^{15}N in the T.C.A.-soluble fraction and T.C.A.-insoluble fraction are identical (see Tables, III, IV, and V). In fact, the identity of ^{15}N contents was observed in experiments in which whole protein and labelled hydrolysate were used. This result would not be expected if faecal nitrogen represented mainly unhydrolysed, unabsorbed dietary protein. The similarity of the labelling of total faecal nitrogen and T.C.A.-soluble nitrogen was also observed after administration of [^{15}N] glycine to a coeliac patient (Table VIII). While incorporation of amino-acids into protein may arise from microbial action, it would seem more likely that this result is explicable by an anabolic process occurring in tissues outside the lumen of the intestinal tract.

Source of Faecal Nitrogen in Adult Coeliac Disease

Since the patients with coeliac disease were not on measured diets during the experiments, the approximate nitrogen intake was calculated from the sum of the urinary and faecal nitrogen. For two three-day periods in two different experiments, the isotope contents expected on the basis of an exclusive dietary origin of faecal nitrogen were 0.084 and 0.058 atoms% excess when whole protein was fed, while the dilutions observed in the faeces were 0.029 and 0.019% respectively. In a further experiment when the hydrolysate was fed, the corresponding figures were 0.058 (calculated) and 0.019% (observed).

It would seem clear, therefore, that the greatly increased faecal nitrogen is, as in the normal, largely of endogenous origin. This conclusion was reached many years ago by McCrudden and Fales (1912, 1913) on the basis of the finding that the amount of nitrogen excreted in the faeces of children with coeliac disease was largely independent of dietary intake. In one experiment recorded here (Table VII) a patient was fed 175 g. of protein per day over six days, and excreted in the faeces on the average 12.6 g. of nitrogen per day. The nature of this nitrogen was not determined, but the suggestion is that in this patient faecal nitrogen was not completely independent of dietary intake.

The question arises regarding the cause of the increased faecal nitrogen found in most patients with adult coeliac disease. One possibility is that absorption of nitrogen in coeliac disease is deficient, as already shown (Crane and Neuberger, 1960b). As the amount of faecal nitrogen is determined by the rates of two normally balanced opposing reactions which are (*a*) the addition of protein and other nitrogenous constituents to the intestinal " pool," and (*b*) the absorption or reabsorption of nitrogenous compounds by the mucosa, it follows that defective absorption will automatically lead to an increased elimination of nitrogen in the faeces. The other possibility is that, owing to the disorganization of the mucosal surface, increased leakage of urea, amino-acids, or proteins into the lumen of the gut takes place and a reduced rate of absorption is unable to cope with this situation. We have no evidence on this point, but it is quite possible, and indeed it has been suggested by Schwartz and Jarnum (1959), that the rate of destruction of plasma protein in the gut in steatorrhoea may be greatly increased. If this hypothesis is correct this would explain the low plasma-protein values found in many cases of steatorrhoea.

In one experiment the amino-acid composition of the faecal protein was examined chromatographically, and it could be shown that essential amino-acids were present in quantities characteristic of protein of high nutritive value. The continuous protein loss occurring in the faeces, especially of protein of high biological value, may be an important factor in causing the protein deficiency observed in these patients, particularly when it is remembered that, apart from nitrogen, there may be a loss of other foodstuffs such as non-absorbed or excreted faecal fat, deficient absorption of mineral elements such as potassium, calcium, and iron, and of vitamins such as folic acid, fat-soluble vitamins, and vitamin B_{12}. A normal person can adapt himself to a daily dietary protein allowance of 50 g., and the effective intake of a patient suffering from coeliac disease, excreting relatively large amounts of nitrogen in his faeces, is generally not smaller than this figure. It is likely that it is the combination of protein loss with a caloric deficiency and defective absorption of essential nutrients which causes the inanition and reduction in body protein which are so often found in the chronic stages of coeliac disease. It is also possible that reduced caloric intake, together with the more specific dietary deficiencies, prevents the adaptation to low nitrogen intake to be made which can be performed by the normal subject.

SUMMARY

Yeast protein labelled with the heavy nitrogen isotope ^{15}N was fed to normal individuals, and the total excretion of labelled nitrogen in the urine and in the faeces was measured over varying periods of time. The faecal nitrogen was also partitioned into protein N (T.C.A.-insoluble) and non-protein N (T.C.A.-soluble). Enzymic hydrolysates consisting mainly of amino-acids of the labelled protein were also given. The labelling of the faecal nitrogen was found to be less than would have been expected if it were to consist entirely of unhydrolysed dietary protein. Moreover, the extent of labelling and the distribution of the labelled nitrogen between T.C.A.-soluble and T.C.A.-insoluble fractions were identical in the experiments in which labelled protein and labelled protein hydrolysate were given. It is concluded that a large part, possibly more than half, of the faecal nitrogen is derived from endogenous sources such as gastric juice, pancreatic secretion, succus entericus, urea, and other compounds, possibly even including plasma proteins which have leaked out from the systemic circulation throught the gut wall.

The total nitrogen in the faeces was increased in all the patients with coeliac disease examined, and the value for the isotope eliminated through faeces was also greatly enhanced. The general pattern of labelling suggested that, as in the normal, a large part of the faecal nitrogen was endogenous. In one patient faecal nitrogen was particularly high on a normal diet, and on increasing protein intake an average daily nitrogen excretion of over 12 g. was recorded. The possibility is discussed that in this and other cases the abnormally high nitrogen excretion may be due to a combination of deficient absorption or reabsorption and a leakage of endogenous constituents ultimately derived from the plasma. It is suggested that this loss of nitrogen through the faeces

adds considerably to the nutritional deficiency caused by loss of calories and defective absorption of mineral elements and vitamins, which are known to be associated with steatorrhoea of long standing.

We wish to express our gratitude to Sir Charles Harington, F.R.S., and to Dr. A. S. McFarlane for permission to use the mass spectrometer at the National Institute for Medical Research, Mill Hill, and to Mr. G. Dickenson for valuable co-operation in carrying out the very large number of determinations of ^{15}N. We thank Dr. Margot Shiner, of the Gastroenterological Unit, the Central Middlesex Hospital, for performing jejunal biopsies on the patients and for the estimation of duodenal enzymes; Dr. E. Miller of the Distillers Co. Ltd., Great Burgh, Epsom, Surrey, for gifts of yeast cultures; and Miss Sheila Wilkie, late dietitian of St. Mary's Hospital, for supervising the diets of one patient. Our thanks are also due to Professor W. S. Peart, Dr. W. D. W. Brooks, and Dr. T. A. Kemp, of St. Mary's Hospital, and Dr. F. Avery Jones, of the Gastroenterological Unit, the Central Middlesex Hospital, for permission to study patients under their care. We are also indebted to the Board of Governors of St. Mary's Hospital for a grant from endowment funds for the purchase of ^{15}N. Finally, one of us (C. W. C.) wishes to thank the British Medical Association for the award of a scientific scholarship during 1957–8 when a part of this work was carried out.

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Dr. F. TROSS, leader of the World Health Organization's yaws control team in the South Pacific, has made a three-month visit to the Cook Islands, where he conducted a survey and trained staff in the eradication of yaws. Dr. Tross has been working since 1954 in co-operation with local governments in South Pacific territories in a campaign against this disease. It involved the mass treatment of the entire indigenous population of these territories with penicillin, followed by several extensive surveys. As a result the incidence of yaws in Fiji, Western Samoa, British Solomon Islands, Gilbert and Ellice Islands, and the New Hebrides has dropped from an average of 15% to a few residual cases. (N.Z. Release No. A26/60.)

CORRELATION OF RADIOACTIVE AND CHEMICAL FAECAL FAT IN DIFFERENT MALABSORPTION SYNDROMES*

BY

B. D. PIMPARKAR, M.B., B.S.

Assistant Instructor in Gastroenterology, Graduate School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

E. G. TULSKY, M.D.

Assistant Professor of Radiology, Graduate School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

M. H. KALSER, M.D., Ph.D.

Associate Professor of Medicine (Gastroenterology), University of Miami, Florida; Formerly Assistant Professor of Gastroenterology, Graduate School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

AND

H. L. BOCKUS, M.D.

Chairman, Department of Medicine and Gastroenterology, Graduate School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

Many methods of studying fat-absorption from the gastro-intestinal tract have been used. The most accurate method of quantitatively determining faulty assimilation of fat and protein is the balance technique accurately calculating the components in ingested food and chemically determining the residue of the stools (Cooke *et al.*, 1946, 1953; Wollaeger *et al.*, 1947; Annegers *et al.*, 1948; Comfort *et al.*, 1953; Weijers and van de Kamer, 1953; Frazer, 1955; French, 1955; Crowe and Blackburn, 1956; Comfort, 1957; Kalser, 1957). This method has certain disadvantages as a routine clinical diagnostic aid in that it is time-consuming, laborious, and expensive, requiring a metabolic ward and three to five days for the collection of stools. Such facilities are seldom available in the average hospital.

Since the advent of radioisotopes, particularly the ^{131}I labelled fats, the absorption tests in humans are becoming much more common. These tests are relatively simple to perform and may be carried out in any radioisotope laboratory. They do not require the special facilities needed for faecal chemical balance study.

In view of the simplicity of ^{131}I labelled fat studies as against the time-consuming, expensive, and laborious technique of faecal chemical-balance studies, it is important that controlled studies to correlate these two types of tests be done in the same subjects. No such studies to our knowledge were published until those of Grossman and Jordan (1958).

It is the purpose of this project to compare in a large series the accuracy of radioactive ^{131}I labelled triolein studies with faecal chemical intake-excretion studies as a diagnostic aid in the various malabsorption syndromes.

Methods

Twenty-four normal volunteers consisting of members of the house staff and laboratory personnel were studied as normal controls.

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One hundred patients from the gastro-intestinal service of the Graduate Hospital of the University of Pennsylvania who were suspected of having malabsorption were studied. The clinical diagnoses in these 100 patients were as follows: idiopathic steatorrhoea, 10; non-specific regional enteritis, 12; diseases of pancreas, 18; diseases of hepatobiliary system, 15; functional enterocolonopathy, 13; gastric resections, 11; non-specific idiopathic ulcerative colitis, 5; and miscellaneous, 16.

All of the patients had a complete clinical evaluation, including history and physical examination. Appropriate radiological examinations had been performed. Each person also had routine haematological and biochemical examinations (haemograms, fasting blood-sugar, blood urea nitrogen, total proteins with albumin/globulin ratio, serum calcium, prothrombin time, cholesterol, etc.).

Each individual was given 10 min. (0.6 ml.) of Lugol's solution three times a day for two days prior to the test meal to block the thyroid uptake of radioactive ^{131}I. Each was placed on a standard diet containing 100 g. of fat, 120 g. of protein, and 270 g. of carbohydrate per day for about 48 hours prior to the test meal and during the intake-excretion studies. All of the non-consumed diet was returned to the diet kitchen for calculation. In each test it was established that the subject ate at least 50 g. of fat per day. Carmine was used as a marker for the balance study.

The ^{131}I triolein meal was prepared in emulsion and capsule forms according to the methods of Shingleton *et al.* (1957) and Isley *et al.* (1958) respectively. This radioactive triolein meal was administered to the fasting patient about one to two hours after the first dose of carmine was given. Blood was withdrawn every two hours till a peak was reached and the blood radioactivity was determined according to the method of Shingleton *et al.*, except that the blood volume was presumed to be 3,000 ml. per square metre of body-surface area. Stools were collected in a wide-mouthed jar and faecal radioactivity and faecal chemical fat were determined on the same specimen. In each instance stools were collected till the last specimen did not show significant radioactivity. The usual collection period was four days, with a range of three to six days. Blood peak radioactivity was expressed in terms of percentage of the administered dose in the calculated whole blood volume at the time of drawing of the specimen. The faecal radioactivity was expressed as the percentage excretion of the administered dose. The faecal chemical fat was determined by the method of Van de Kamer *et al.* (1949) and expressed as the number of grammes of total fat† excreted per day.

Results

Fig. 1 shows the mean blood peak radioactivity at different times in 20 normal volunteers who had both emulsion and capsule types of the triolein meal. The absorptive pattern after the emulsion meal was much more uniform, with a narrower range of values than that with the capsule type of meal. Although the mean peak occurred at four hours with each type of meal, there were four volunteers in whom the peak did not occur until 10 hours after the capsule meal. Fig. 2 shows the mean values after the emulsion and the capsule meals and after both meals together in 45 tests on 24 normal volunteers. Since the peak level is the most important value in the blood absorptive pattern, only these values are considered in the subsequent discussion. The mean blood peak radioactivity value in 45 tests on 24 normal volunteers after the emulsion and capsule meals was 19 $\pm$ 5% of administered dose with a range of 10 to 32% of the administered dose and a calculated lower limit of normal (mean $\pm$ 2 S.D.) of 9% of the administered dose in the whole blood volume.

The mean faecal radioactivity value in 31 experiments on 20 normal volunteers was 3 $\pm$ 1.94% of the administered dose with a range of 1 to 9% of the administered dose and a calculated upper limit of normal (mean $\pm$ 2 S.D.) of 6.9% of the administered dose.

The mean faecal chemical fat value in the same 31 specimens on 20 normal volunteers was 4 $\pm$ 1.6 g. per

†Fat is used in its broadest sense, and means the total neutral fat, excluding sterols and phospholipid.

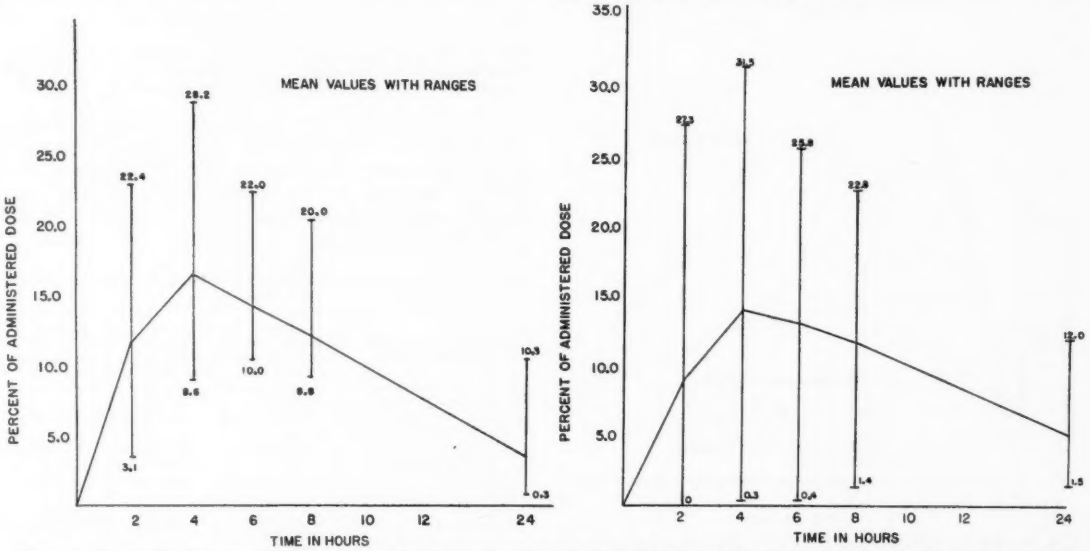

FIG. 1.—Mean blood peak radioactivity in 20 volunteers with emulsion of ^{131}I triolein (left) and with capsule of ^{131}I triolein (right).

day with a range of 2 to 9 g. per day and a calculated upper limit of normal (mean ± 2 S.D.) of 7.2 g. per day.

In the subsequent discussion 7% of the administered dose as faecal radioactivity and 7 g. per day of faecal chemical fat have been taken as the upper limit of normal for the stool studies, while 9% of the administered dose in the whole blood volume at any time has been taken as the lower limit of normal blood peak radioactivity.

During this study 115 tests were performed on 102 patients and these are analysed in the following discussion. Some of these patients had these studies on two occasions at an interval of one month to one year. Their clinical condition was changed because of the specific or non-specific medical therapy, and hence each test is regarded as a separate patient.

In Figs. 3, 4, and 5 the blood absorptive pattern of normals is compared with that of patients with different types of malabsorption syndromes. From these figures it will be seen that the absorptive pattern was nearly

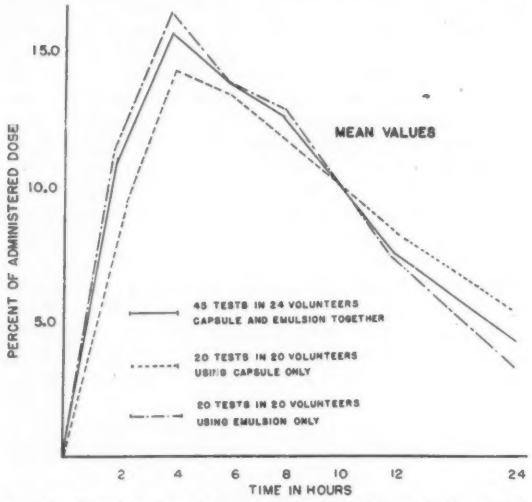
15.0
10.0
5.0
PERCENT OF ADMINISTERED DOSE
MEAN VALUES
45 TESTS IN 24 VOLUNTEERS CAPSULE AND EMULSION TOGETHER
20 TESTS IN 20 VOLUNTEERS USING CAPSULE ONLY
20 TESTS IN 20 VOLUNTEERS USING EMULSION ONLY
2 4 6 8 10 12 24
TIME IN HOURS

FIG. 2.—Blood radioactivity after the emulsion and the capsule meals.

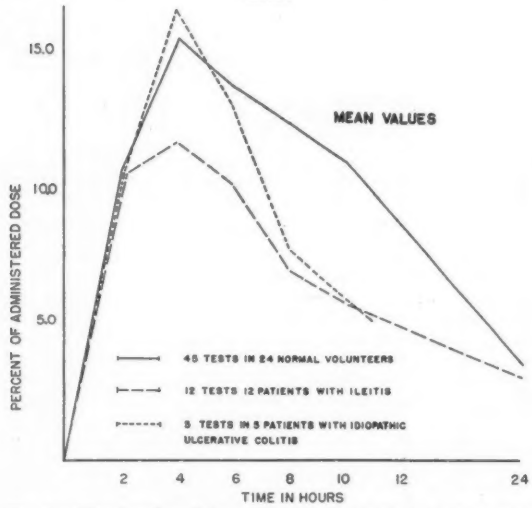
15.0
10.0
5.0
PERCENT OF ADMINISTERED DOSE
MEAN VALUES
45 TESTS IN 24 NORMAL VOLUNTEERS
12 TESTS 12 PATIENTS WITH ILEITIS
5 TESTS IN 5 PATIENTS WITH IDIOPATHIC ULCERATIVE COLITIS
2 4 6 8 10 12 24
TIME IN HOURS

FIG. 3.—Blood radioactivity after oral ^{131}I triolein in patients with ileitis and with idiopathic ulcerative colitis, compared with normal volunteers.

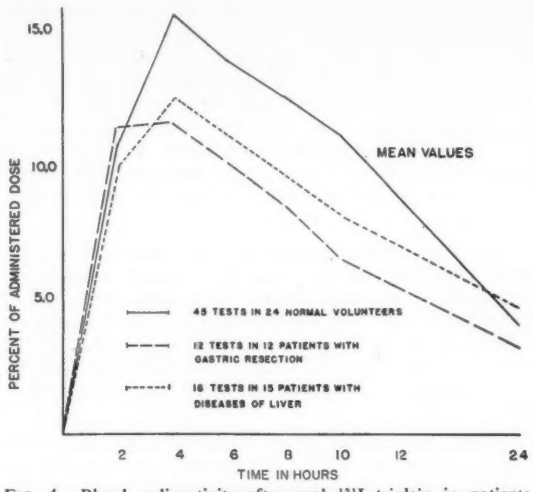
15.0
10.0
5.0
PERCENT OF ADMINISTERED DOSE
MEAN VALUES
45 TESTS IN 24 NORMAL VOLUNTEERS
12 TESTS IN 12 PATIENTS WITH GASTRIC RESECTION
16 TESTS IN 15 PATIENTS WITH DISEASES OF LIVER
2 4 6 8 10 12 24
TIME IN HOURS

FIG. 4.—Blood radioactivity after oral ^{131}I triolein in patients with gastric resection and with liver diseases, compared with normal volunteers.

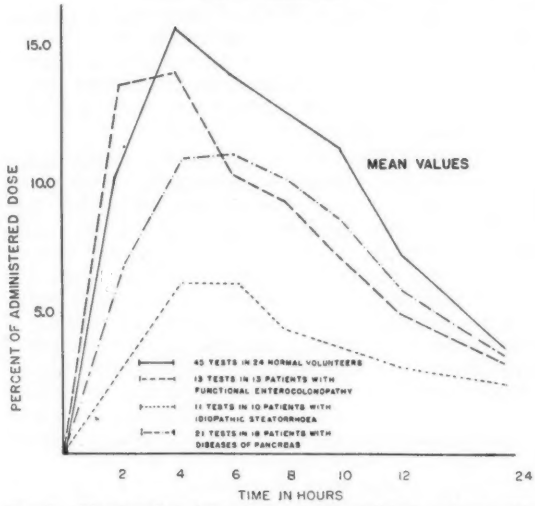
15.0
10.0
5.0
PERCENT OF ADMINISTERED DOSE
MEAN VALUES
45 TESTS IN 24 NORMAL VOLUNTEERS
13 TESTS IN 13 PATIENTS WITH FUNCTIONAL ENTEROCOLONOPATHY
11 TESTS IN 10 PATIENTS WITH IDIOPATHIC STEATORRHOEA
21 TESTS IN 18 PATIENTS WITH DISEASES OF PANCREAS
2 4 6 8 10 12 24
TIME IN HOURS

FIG. 5.—Blood radioactivity after oral ^{131}I triolein in patients with functional enterocolonopathy, with idiopathic steatorrhoea, and with diseases of pancreas, compared with normal volunteers.

normal in patients with non-specific ulcerative colitis and in patients with functional enterocolonopathy, while it was moderately impaired in patients with pancreatic disease, diseases of the hepatobiliary system, non-specific regional ileitis, and gastric resection. It was markedly impaired only in idiopathic steatorrhoea.

TABLE I.—*Blood Peak Radioactivity Values in Different Groups of Patients*

Name of Group and Total No. in Each	Mean Blood Peak Radioactivity, with S.D.	Range in the Blood Peak Radioactivity	Difference from the Normals, p Value
Normal volunteers, 24 ..	19·0±5·0	10·0–32·0	—
Idiopathic steatorrhoea, 15	7·5±5·1	1·0–17·0	<0·001
Non-specific regional enteritis, 12	12·8±6·7	1·0–25·0	<0·01
Diseases of pancreas, 25 ..	11·6±6·6	1·0–24·0	<0·001
Diseases of hepatobiliary system, 18	13·3±8·3	1·0–21·0	<0·01
Functional enterocolonopathy, 13	17·1±6·5	7·0–31·0	<0·2
Gastric surgery, 11 ..	13·0±5·5	3·0–20·0	<0·01
Non-specific ulcerative colitis, 5	16·2±7·2	12·0–21·0	<0·5

Table I shows the mean blood peak radioactivity values in the various groups with standard deviations and ranges. Attention is called to the last column in that table, which shows the differences from the normal. The p value was considered significant if it was less than 0.05. It was significant in all groups except functional enterocolonopathy and non-specific ulcerative colitis.

TABLE II.—*Faecal Radioactivity Values in Different Groups of Patients*

Name of Group and Total No. in Each	Mean Faecal Radioactivity with S.D.	Range in the Faecal Radioactivity	Differences from the Normals, p Value
Normal volunteers, 24	3·0 ± 1·94	1·0– 9·0	—
Idiopathic steatorrhoea, 15	29·1 ±22·7	1·0–63·0	<0·001
Non-specific regional enteritis, 12	22·8 ±22·2	1·0–68·0	<0·001
Diseases of pancreas, 25	18·8 ±26·7	1·0–95·0	<0·02
Diseases of hepatobiliary system, 18	15·6 ±23·3	1·0–87·0	<0·05
Functional enterocolonopathy, 13	1·92± 1·5	1·0– 5·0	<0·05
Gastric surgery, 11	12·8 ±19·3	1·0–67·0	<0·05
Non-specific ulcerative colitis, 5	9·6 ± 7·3	1·0–17·0	<0·01

Table II shows the mean faecal radioactivity values in different groups, with their corresponding standard deviations and ranges. The mean faecal radioactivity was significantly different from the normals in all groups except functional enterocolonopathy.

TABLE III.—*Faecal Chemical Fat Values in Different Groups of Patients*

Name of Group and Total No. in Each	Mean Faecal Chemical Fat with S.D.	Range in Faecal Chemical Fat Values	Difference from the Normals, p Value
Normal volunteers, 24	4·0± 1·6	2·0– 9·0	—
Idiopathic steatorrhoea, 15	22·3±13·7	7·0–59·0	<0·001
Non-specific regional enteritis, 12	23·2±23·0	1·0–66·0	<0·001
Diseases of pancreas, 25	11·2±13·2	2·0–51·0	<0·02
Diseases of hepatobiliary system, 18	16·3±11·7	3·0±44·0	<0·001
Functional enterocolonopathy, 13	2·8± 1·6	1·0– 6·0	<0·05
Gastric surgery, 11	9·5± 9·2	1·0–29·0	<0·02
Non-specific ulcerative colitis, 5	3·8± 1·9	2·0– 7·0	<1·0

Table III demonstrates the mean faecal chemical fat values in different groups with their corresponding standard deviations and ranges. The mean faecal chemical fat was significantly abnormal in all groups except those with non-specific ulcerative colitis and functional enterocolonopathy. The faecal chemical fat was significantly lower than normal in patients with functional enterocolonopathy.

Table IV shows the results of the three studies in all of the groups with the patients classified into normals and abnormals according to the criteria described previously.

In each division except for the ulcerative colitis and miscellaneous groups more patients were abnormal percentage wise by the faecal chemical fat determination, intermediate by the faecal radioactivity determination, and least by the blood peak radioactivity determination. For the detection of steatorrhoea the faecal chemical fat determination was the most sensitive, followed by the faecal radioactivity determination and then the blood peak radioactivity determination. Of the three tests there was much better correlation between the faecal chemical fat test and the faecal radioactivity test than between any other two tests.

When only normals are considered (Table IV) the opposite is seen—that is, there were more people who had normal faecal and blood radioactivity as compared with a faecal chemical fat.

These results suggest that ^{131}I triolein studies are not as sensitive a diagnostic aid in detection of steatorrhoea as is the faecal chemical fat determination.

When the values for faecal chemical fat, faecal radioactivity, and blood peak radioactivity were all normal, or were all abnormal, we defined this as complete agreement of the three tests. On the other hand, if the faecal chemical fat was normal and both blood peak and faecal radioactivity were abnormal, or vice versa (abnormal faecal chemical fat with normal blood peak and faecal radioactivity), we defined this as complete disagreement of the three tests.

With the use of these criteria in analysing the 115 patients (Table V) there was complete agreement in 74 patients or in 64% and there was complete disagreement in 13%. Table VI shows the incidences of complete agreement and complete disagreement in all the groups. It should be noted that the incidence of complete agreement varied from 40 to 93%, with a mean of 62%, while

TABLE V.—*Correlation of Faecal Chemical Intake–Excretion Studies and ^{131}I Triolein Test in* 115 *Patients as a Whole Group*

		Faecal Chemical Fat			
		Normal 7 g. Day		Abnormal 7 g./Day	
	Total No. 115	No.	%	No.	%
		61	53	54	47
Faecal radioactivity % adm. dose	Normal, 7%	51	84	13	24
	Abnormal, 7%	10	16	41	76
Blood peak radioactivity	Normal, 9%	54	89	24	46
	Abnormal, 9%	7	11	30	54
Combined faecal and blood peak radioactivity	Both normal	47	77	11	21
	One or both disagree	14	23	27	50
	Both abnormal	4	7	27	50

TABLE IV.—*Normal and Abnormal Results by Three Tests in Different Groups of Patients*

Name of Group and Total Cases in Each	Faecal Chemical Fat				Faecal Radioactivity				Blood Peak Radioactivity			
	Normal ≤7 g./Day		Abnormal >7 g./Day		Normal ≤7%		Abnormal >7%		Normal ≥9%		Abnormal <9%	
	Tests		Tests		Tests		Tests		Tests		Tests	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
115 tests as a whole irrespective of clinical diagnosis	61	53	54	47	64	56	51	44	78	68	37	32
Idiopathic steatorrhoea, 15	1	7	14	93	4	27	11	73	5	33	10	66
Non-specific regional enteritis, 12	4	33	8	66	5	42	7	58	9	66	3	33
Diseases of pancreas, 25	15	60	10	40	15	60	10	40	16	64	9	36
,, ,, liver, 18	5	28	13	72	11	61	7	39	12	66	6	33
Functional enterocolonopathy, 13	13	100	0	0	13	100	0	0	12	92	1	8
Gastric surgery, 11	6	55	5	45	6	55	5	45	8	73	3	27
Non-specific idiopathic ulcerative colitis, 5	5	100	0	0	2	40	3	60	5	100	0	0
Miscellaneous, 16	12	75	4	25	8	50	8	50	11	69	5	31

TABLE VI.—*Complete Agreement and Complete Disagreement Between Faecal Chemical Fat Determination and Faecal and Blood Peak Radioactivity Determination*

Name of Group	Percentage of Complete Three Tests	
	Agreement	Disagreement
Idiopathic steatorrhoea	66	14
Non-specific regional enteritis	58	8
Diseases of pancreas	72	4
,, ,, hepatobiliary system	50	33
Functional enterocolonopathy	93	0
Gastric surgery	58	0
Ulcerative colitis	40	0
Miscellaneous	56	25
Mean	62	10·4
115 patients as a whole group	64	13

the incidence of complete disagreement ranged from 0 to 33%, with a mean of 10%. Thus there was complete agreement in about two-thirds and complete disagreement in another one-eighth, so that about one-third of the patients were either false positive or false negative.

When, in a given patient, the faecal chemical fat was abnormal and the faecal radioactivity and/or blood peak radioactivity was in the range of normal, this patient was said to be false negative. On the other hand, if the chemical fat was normal and the faecal and/or blood peak radioactivity was abnormal then this patient was a false positive for steatorrhoea.

TABLE VII.—*Percentage False Negative by ^{131}I Triolein Test as Compared with Faecal Intake-Excretion Studies*

Name of Group	Percentage of False Negative		
	By Blood Peak Radioactivity	By Both	By Faecal Radioactivity
Idiopathic steatorrhoea	29	14	21
Non-specific regional enteritis	63	12	12
Diseases of pancreas	40	10	10
,, ,, hepatobiliary system	54	46	54
Gastric surgery	60	0	0
Ulcerative colitis	0	0	0
Miscellaneous	50	25	25
Mean	43	14	17
115 patients as a whole group	46	21	24

Table VII shows the incidence of false negatives in different groups of patients by the blood peak radioactivity test alone, by the faecal radioactivity test alone, and by both tests together. The incidence of false negatives by blood peak radioactivity tests ranged from 0 to 63%, with a mean of 43% in the different groups and 46% in the 115 patients as a whole group. The incidence of false negatives by faecal radioactivity tests ranged from 0 to 54%, with a mean of 17% in different groups and 24% in the whole group of 115 patients. The differences between blood peak radioactivity test and faecal radioactivity test are quite significant. Also, when both blood peak radioactivity and faecal radioactivity are considered, the incidence of false negatives ranged from 0 to 46%, with a mean of 14% in different groups and 21% in the 115 patients as a whole group.

These results suggest that the triolein test is likely to be abnormal in patients with steatorrhoea in about 50% by blood peak, in 75% by faecal radioactivity tests, and in about 80 to 85% by both faecal and blood peak radioactivity tests.

Table VIII shows the incidence of false positives in the different groups. The incidence of false positives by the blood peak radioactivity test ranged from 0 to 25% with a mean of 8.5% in different groups and 11% in the whole group of 115 patients. The incidence of false positive by the faecal radioactivity test ranged from 0 to 60%, with a mean of 16% in different groups and 16% in the entire series of 115 patients. When the false-positive patients in the ulcerative colitis group, where exudation of protein and inorganic ^{131}I into the colon which may account for the increased radioactivity are omitted, the mean incidence of false positives by faecal radioactivity is the same as that by blood peak

TABLE VIII.—*Percentage False Positive by ^{131}I Triolein Test as Compared with Faecal Intake-Excretion Studies*

Name of Group	Percentage of False Positive		
	By Blood Peak Radioactivity	By Both	By Faecal Radioactivity
Idiopathic steatorrhoea	0	0	0
Non-specific regional enteritis	0	0	0
Diseases of pancreas	20	0	6
,, ,, hepatobiliary system	0	0	20
Functional enterocolonopathy	7	0	0
Gastric surgery	16	0	0
Ulcerative colitis	0	0	60
Miscellaneous	25	25	42
Mean	8·5	3·0	16·0
115 patients as a whole group	11	7	16

radioactivity—namely, 9%. On the other hand, when both faecal and blood peak radioactivity are taken into consideration, the incidence of false-positive tests ranges from 0 to 25%, with a mean of 3% in different groups and 7% in the entire group.

These results suggest that the triolein test is likely to be normal in about 80 to 95% of patients who do not have steatorrhoea, if both blood peak and faecal radioactivity are determined, while if blood peak radioactivity alone is determined it is likely to be normal in about 85 to 90%. If only faecal radioactivity is determined, the study is likely to be normal in about 80 to 85%. When Tables VII and VIII are compared it is seen that the incidence of false-positive results is much less than the incidence of false-negative results by either blood peak radioactivity or a faecal radioactivity, or by both tests. This finding again suggests that the radioactive triolein studies are not as sensitive an index of steatorrhoea as is the faecal chemical fat determination.

Discussion

The use of radio-iodinated ^{131}I fat in the investigation of indigestion and absorption involves some important sources of error. In determining the efficiency of the labelled-fat meal it must be remembered that one is using a fat which is not usually present in such amounts in the diet. The iodine is partly split off from the organic compound both in the intestinal contents by the action of bacterial enzymes and in the cells after absorption. ^{131}I exists in the blood in two forms after the ingestion of the labelled triolein. The bulk of the radioactivity is present as inorganic ^{131}I; the remainder is bound to lipid. This lipid-bound ^{131}I represents the ingested fat which is in transport in the blood as lipoprotein and chylomicrons. The lipid fraction usually contains 20 to 35% of the whole blood radioactivity, though the range extends from 0 to 50% (Beres *et al.*, 1957; Turner, 1958). The absorbed ^{131}I is excreted mainly by the kidneys as inorganic ^{131}I.

Beres *et al.* found that normally the mean 24-hour urinary excretion was 55 ± 11%, with a range of 24 to 68%. Since this ^{131}I is in the form of inorganic iodide, the value represents the result of several meta-

bolic processes: fat absorption, fat transport, fat utilization, completeness of thyroid blockade, and renal function. Hence it is not possible to get quantitative information from blood-activity studies on the extent and rate of absorption, since both are influenced by the rate of elimination by the kidney, which may vary for inorganic iodide and different organic iodine compounds. However, if the radioactivity in the blood is followed, valuable information may be obtained as regards the time relationship in absorption. The inorganic ^{131}I level is dependent upon the rate of utilization of the fat (at which time the iodine–fatty-acid bond is apparently broken).

Turner (1958) demonstrated that in dogs after feeding a labelled-fat meal the changes in the plasma ^{131}I lipid curves paralleled the changes in the turbidity, but as the quantity of olive oil fed with the ^{131}I triolein was increased there were changes in the plasma turbidity and the ^{131}I lipid activity decreased, while the plasma turbidity increased as the amount of fat was increased. This, however, was not observed in humans (Grossman and Jordan, 1958). Turner also noted differences between young and old dogs in their response to fat administered by the oral and intravenous routes. The plasma ^{131}I lipid activity and turbidity after the ingestion of fat were greatly increased in the old dogs as compared with the young dogs. The elevated levels were shown to be the result of an unexplained decrease in the rate of removal of fat from the blood in the dogs. Van Handel and Zilversmit (1958) studied the validity of ^{131}I labelling of fat by: (*a*) comparing ^{131}I lipid radioactivity with chemically determined fat in the lymph and lipaemic blood, and (*b*) mixing ^{131}I-labelled fat or fatty acid with radioactive-carbon (^{14}C)-labelled fat or fatty acid and determining the ratio of lipid ^{131}I to ^{14}C in lymph fat and in the neutral fat and phospholipid fraction of tissues. Their results confirmed Turner's observations that the ^{131}I-labelled triolein administered intravenously as an emulsion disappears from the blood at the same rate as neutral fat, although differences were seen in the lymph.

After the oral administration of ^{131}I triolein the concentration of ^{131}I triglyceride in the dog plasma during the period of alimentary hyperlipaemia is lower than that of the chemically determined fat. This difference between the specific activity of fed fat and plasma fat already exists in the lymph as shown by the low specific activity of dog and rat lymph compared with that of the administered fat. Comparison of ^{131}I and ^{14}C triolein showed that dilution by an endogenous triglyceride pool cannot account for the absorbed decrease in specific activity. Those authors state that ^{131}I triolein does not appear to give a quantitative measure of the amount of fat absorbed no matter whether part of the ^{131}I is broken off the fat or whether ^{131}I triolein is absorbed at a rate different from triolein. This finding does not, however, affect the use of ^{131}I triolein as an empiric clinical test for the malabsorption syndrome.

Grossman and Jordan (1958) report normal blood radioactivity in 10 patients or 71% of 14 patients with pancreatic steatorrhoea. All 14 patients had abnormal faecal radioactivity. Beres *et al.* (1957) also found this discrepancy between blood radioactivity and faecal radioactivity in cases of pancreatic disease, liver disease, gastric surgery, and regional enteritis. McKenna *et al.* (1957) concluded that although the blood curve is a good indicator of the absorption rate, the stool recovery of ^{131}I is a better indicator of the total absorption of the labelled fat. Beres *et al.* (1957), McKenna *et al.* (1957), and Berkowitz and Sklaroff (1957) found variable absorption patterns in patients with gastric resections. In this group 40 to 60% of the patients had abnormally low values.

The question of origin of faecal fat is not definitely settled. There are two sources of faecal fat: endogenous (Hill and Bloor, 1922; Sperry and Bloor, 1924; Sperry, 1926, 1932; Sperry and Angevine, 1932; Bloor, 1943; Norcia and Lundberg, 1954) and exogenous (Wollaeger *et al.*, 1947; Annegers *et al.*, 1948; Crowe and Blackburn, 1956; Crowe *et al.*, 1956; Asenjo *et al.*, 1957).

So far as the faecal analysis of radioactivity is concerned, the enterohepatic circulation of iodine as well as the secretion of ^{131}I lipid into the gut should be taken into consideration. Beres *et al.* (1957) report that only 0.5% of the administered dose was recovered in the four-day collection of bile in the patient with a biliary fistula. This is quite insignificant and would not affect the final analysis of faecal radioactivity. Whether there is any secretion of ^{131}I lipid into the gastro-intestinal tract remains to be studied.

Further, the sources of error by contamination of faeces by urine can be very great in the ^{131}I triolein tests, as a large quantity of ^{131}I is excreted by the kidney in the first 24 hours. If there is only minimal contamination of faeces by urine, faecal radioactivity will be greatly increased. In our studies we tried to exclude all those patients in whom the faeces might have been contaminated with urine. Moreover, in general there were more false-positive or false-negative results with the blood peak radioactivity determination than by the faecal radioactivity study. Also, with a few exceptions, faecal nitrogen was increased only when faecal chemical fat was also increased. These two facts may indicate that there was no urinary contamination of faeces in our series.

Summary and Conclusions

The accuracy of the radioactive ^{131}I-labelled triolein test and the faecal chemical balance studies as a diagnostic aid in the various malabsorption syndromes is compared in a series of 24 normal volunteers and 102 patients suspected of having malabsorption.

Blood peak radioactivity, faecal radioactivity, and faecal chemical fat were determined in 160 tests, 146 tests, and 146 tests respectively, performed on 126 persons. These consisted of the following groups: normal volunteers, 24; idiopathic steatorrhoea, 10; non-specific regional enteritis, 12; diseases of pancreas, 20; diseases of hepatobiliary system, 15; functional enterocolonopathy, 13; gastric surgery, 11; non-specific idiopathic ulcerative colitis, 5; and a miscellaneous group of 16 patients.

The mean blood peak radioactivity in 45 tests on 24 normal volunteers was 19 $\pm$ 5% of the administered dose, with a calculated lower limit of normal (mean $\pm$ 2 S.D.), being 9% of the administered dose. The mean faecal radioactivity in 31 tests on 20 normal volunteers was 3 $\pm$ 1.94% of the administered dose, with a range of 1 to 9% of the administered dose and with a calculated lower limit of normal (mean $\pm$ 2 S.D.) being 6.9% of the administered dose. The mean faecal chemical fat in the same 31 tests was 4 $\pm$ 1.6 g. per day, with a range of 2 to 9 g. per day and a calculated upper limit of normal (mean $\pm$ 2 S.D.) being 7.2 g. per day.

In general, in each group of those who had abnormal faecal chemical fat the faecal radioactivity determination was abnormal in about 75%, while the blood peak radioactivity was abnormal in only about 50%. On the other hand, in nearly each group, of those who had normal faecal chemical fat, nearly 80% had a normal faecal radioactivity, while the blood peak radioactivity was normal in nearly 85%.

Of the two ^{131}I triolein determinations the faecal radioactivity determination was found to be a much better index of the presence of steatorrhoea than the blood peak radioactivity test. When both studies were carried out the index of accuracy was increased.

If a patient has normal blood peak and faecal radioactivity values after the ^{131}I triolein meals, the chances of his being normal are about 85 to 95%, while the chance of his having steatorrhoea (false negative) are about 15 to 25%. On the other hand, if both values are abnormal the chances of his being normal are about 10% (false positive), while the chances of his having steatorrhoea are about 75%.

Administration of the ^{131}I-labelled triolein does not afford an adequate quantitation of steatorrhoea, as does the faecal chemical balance study.

Although the ^{131}I triolein studies are good, simple exploratory tests in the detection of steatorrhoea, particularly if both faecal and blood peak radioactivity are determined, show by our results that ^{131}I triolein is not as sensitive an index of accuracy in the detection of steatorrhoea as is the faecal chemical fat determination. However, if facilities for metabolic balance studies are not available, then because of its simplicity the triolein test (using both blood peak and faecal radioactivity determination) may be used as a diagnostic aid in the detection of steatorrhoea, provided its limitations are fully appreciated.

It is also recommended that, in a given patient, if both blood peak and faecal radioactivity are abnormal, that patient should have faecal chemical balance studies to establish the diagnosis definitely and for the quantitative estimation of steatorrhoea.

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STAPHYLOCOCCAL SEPSIS IN OUT-PATIENTS

RELATION OF PENICILLIN RESISTANCE TO PREVIOUS CONTACT WITH HOSPITALS

BY

D. A. MACFARLANE, M.Ch., B.Sc., F.R.C.S.

J. S. MURRELL, M.B., B.S.

R. A. SHOOTER, M.D.

AND

M. P. CURWEN, M.A.

From the Departments of Surgery, Bacteriology, and Statistics, St. Bartholomew's Hospital, London

It is in hospital that the majority of antibiotic-resistant bacteria are thought to originate. For *Staphylococcus aureus* there is abundant evidence that patients, and babies born in hospital, may become nasal carriers of penicillin-resistant staphylococci and may take resistant staphylococci home. Additional and rather different support for the view that hospitals are the main source of penicillin-resistant staphylococci has been put forward recently by Galbraith (1960). Working with septic patients in general practice, he was able to relate the presence of penicillin-resistant staphylococci in lesions to previous hospital contacts. Similarly, McDonald *et al.* (1960) in a study of recruits joining the Royal Air Force concluded that the high proportion of penicillin-resistant staphylococci carried by men with a history of recent admission to hospital or contact with a baby born in hospital could be attributed to acquisition of staphylococci from hospital.

From this hospital over the last ten years we have reported the increasing proportion of out-patients infected with penicillin-resistant strains of *Staph. aureus*. In this paper we describe our most recent findings and also the results of a survey undertaken to determine if patients with resistant staphylococci had previously been in direct or indirect contact with hospitals.

Materials and Methods

The patients in the survey comprised 208 unselected out-patients attending the casualty department with acute infections of the skin and subcutaneous tissues between October, 1959, and March, 1960. In addition, there were 214 patients with other non-septic conditions, such as lacerations and contusions, attending the same casualty

department during this period. Patients attending other departments in the hospital were excluded from both groups.

Swabs were taken from the lesions of the septic patients as soon as possible. In 85% they were taken immediately after incision; from the rest they were taken at the first attendance or as soon as the lesion discharged. Abscesses accounted for 57% of the septic lesions and boils for 19%. Nasal swabs were taken at the first attendance of septic and non-septic patients; patients in each group were asked for details of recent personal or family hospital contacts.

Bacteriology.—Swabs were cultivated on horse-blood–agar plates. Staphylococci which coagulated plasma in tube were regarded as *Staph. aureus*. Sensitivities to penicillin and tetracycline were determined for all the staphylococci isolated by the cup-plate method.

Results

Antibiotic Sensitivities of Staphylococci from Septic Patients

Coagulase-positive staphylococci were isolated from the lesions of 170 of the patients with sepsis: 67 (39%) of the strains were resistant to penicillin and 103 (61%) were sensitive. Table I shows how these proportions compare with previous published findings from this hospital.

TABLE I.—*Sensitivity to Penicillin of Strains of Staph. aureus from Lesions of Septic Out-patients, 1949–60*

Reference	No. of Strains	Resistant to Penicillin
Griffiths *et al.* (1949) }	261	6%
,, ,, (1950) }		
Birnstingl *et al.* (1952)	200	16%
Rees *et al.* (1955)	200	21%
Burn *et al.* (1957)	218	25%
Present series	170	39%

Five strains were resistant to tetracycline in addition to being resistant to penicillin. They were all sensitive to chloramphenicol and erythromycin. One strain was resistant to tetracycline but sensitive to penicillin.

Penicillin Resistance of Staphylococci from Sepsis in Relation to the Patient's History

Patients were asked if they had attended any hospital in the past 12 months, if their family included any babies born in hospital within the last 12 months, if any other members of the family had been in-patients within the last 12 months, and if they had been given antibiotics by their own doctor in the past three months. The results are set out in Table II. The largest group of patients with a positive contact history was that of 65 who had been out-patients (but not in-patients) during the previous 12 months; penicillin-resistant strains were isolated from 33 (49%) of these patients. Even higher rates were recorded among the other small groups with recent contact, and the patients who had been given an antibiotic by their own doctor. Patients who answered "Yes" to any of these questions had 52% of their staphylococci resistant to penicillin, whereas those who answered "No" to all the questions had only 24% of their staphylococci resistant. All the patients with staphylococci resistant to penicillin and tetracycline had a history of personal or family hospital contact.

TABLE II.—*Penicillin Resistance of Staph. aureus Isolated from Lesions of Patients with Sepsis in Relation to the Patient's History*

	Total	Resistant to Penicillin
All septic patients	170	39%
Patients attending any hospital in last 12 months:		
As an in-patient	13	69%
,, out-patient*	65	49%
With family with baby born in hospital in last 12 months	13	62%
With any other member of family as in-patient in last 12 months	24	58%
Having been given antibiotic by own doctor in past 3 months	20	65%
Patients in one or more of above categories	94	52%
,, ,, none of above categories	76	24%

* Excluding those who were also in-patients.

Of the 170 septic patients no fewer than 65 had had a similar lesion within the previous 12 months. The penicillin-resistance rate of their staphylococci was 40%. For 53 of the patients chemotherapy was begun before the lesion was incised. Their staphylococcal resistance rate was 45%.

Nasal Carriage of Staph. aureus by Septic and Non-septic Patients

Table III sets out the proportion of septic and non-septic patients who were found to be carrying *Staph. aureus* in the nose, and the sensitivity of the staphylococci to penicillin. Carriage rates were almost twice as high in the septic as in the non-septic patients, and the resistance rates were increased.

TABLE III.—*Nasal Carriage of Staph. aureus by Septic and Non-septic Patients*

	Total	Nasal Carriers	Staphylococci Resistant to Penicillin
Septic patients	170	71%	42%
Non-septic ,,	214	34%	32%

For the patients with sepsis there was some correlation between the nasal and infecting staphylococci. Of the 170 patients, 49 were not nasal carriers at the time of swabbing. Of the remainder, 70 carried penicillin-sensitive staphylococci in the nose, and of these 64 were infected with sensitive staphylococci. Fifty-one patients carried penicillin-resistant staphylococci, and of these patients 44 were infected with resistant staphylococci.

Although the nasal carriage rate was lower among the non-septic patients, the carriage rate was greater for the non-septic patients with hospital contacts, as defined earlier, or a history of antibiotic therapy, than for the patients without such a history. The penicillin-resistance rate for the first group was almost double that of the second group (Table IV).

TABLE IV.—*Penicillin Resistance of Staph. aureus Isolated from the Noses of Non-septic Patients*

	Total	Nasal Carriers	Staphylococci Resistant to Penicillin
Patients with hospital contact or previous history of antibiotic treatment	100	39%	41%
Patients without hospital contact or previous history of antibiotic therapy	114	28%	21%

Septic Patients from Whose Lesions Staph. aureus was Not Isolated

There were 38 patients from whose lesions staphylococci were not isolated. In some cases this failure may have been due to technical reasons. That this may not have been responsible for the majority is suggested by the finding that the nasal carriage and the penicillin-resistance rates of this group of patients approximated closely to the rates for the non-septic patients (34% and 31% respectively).

Discussion

The proportion of staphylococci resistant to penicillin responsible for sepsis in out-patients attending this hospital is still increasing. The increase presumably reflects the continued use of penicillin in hospital and general practice, and while this continues there is little reason to expect that the proportion of resistant staphylococci will fall. For infections of the skin and subcutaneous tissues this may not be of great importance, as there is evidence that these conditions perhaps respond to treatment with penicillin, even if caused by penicillin-resistant staphylococci (Burn *et al.*, 1957). More serious infections, however, do not react in this way. A penicillin-resistance rate of 39% implies that penicillin should not be used for the treatment of dangerous staphylococcal infections initially until the results of sensitivity tests are known.

Within hospital, patients who are nasal carriers of staphylococci seem to be more prone to sepsis than those who are not carriers, and the staphylococci responsible can frequently be isolated from the patient's nose before the onset of sepsis (Williams *et al.*, 1959). In our patients, 71% of those with sepsis were nasal carriers as compared with 34% of those without sepsis. That the nasal and septic staphylococci may in most cases have been the same was perhaps suggested by the observation that only 13 (8%) of the patients had a sensitive organism in the nose and a resistant one in the lesion, or *vice versa*. These figures suggest that, outside hospital, sepsis occurs more often in carriers than in non-carriers; but to establish this hypothesis would need a survey of a different kind.

As our survey was conducted on somewhat different lines from those of Galbraith (1960) and McDonald *et al.* (1960), a direct comparison cannot be made. Our results agree in that for staphylococci isolated from patients with sepsis and for staphylococci carried by patients without sepsis the penicillin-resistance rates were considerably higher for the staphylococci belonging to patients with direct or indirect hospital contacts.

Rycroft and Williams (1960) described the high carriage rates of penicillin-resistant staphylococci in children under 6 months who had been born in hospital, an increase which continued at a lower level up to 4 years. They concluded that their results drew attention once more to the part that hospital infection may play in seeding the population with antibiotic-resistant staphylococci. We believe that our results do the same.

Summary

One hundred and seventy strains of *Staph. aureus* have been isolated from out-patients with sepsis. Of these, 39% were found to be resistant to penicillin, the highest figure yet recorded at this hospital and nearly double that reported in 1955.

Patients with a history of hospital contacts or treatment with an antibiotic were more often infected with or carried staphylococci resistant to penicillin than those with no such history. It is suggested that this is a further illustration of the part played by hospital infections in seeding the population with antibiotic-resistant staphylococci.

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CLINICAL EVALUATION OF METRONIDAZOLE

A NEW SYSTEMIC TRICHOMONACIDE

BY

LESLIE WATT, M.D.
Consultant Venereologist

AND

R. F. JENNISON, M.D., M.R.C.P.
Consultant Clinical Pathologist
St. Mary's Hospital for Women, Manchester

Infestation with *Trichomonas vaginalis* causes much distress to many women of all ages. The incidence of the condition in the population as a whole is difficult if not impossible to determine. In this country, in recent years, *T. vaginalis* was found in 5.3% of 562 women attending a birth-control clinic (Whittington, 1951), in 12.8% of 400 women attending a gynaecological department, and in 21.3% of 400 women attending a venereal disease clinic (Whittington, 1957). These figures represent the incidence in highly selected groups of patients and do not take into account the women who are treated by their own practitioners and those who, for reasons of modesty or fear, prefer to suffer in silence rather than seek advice. Apart from the often considerable physical discomfort, much psychological upset occurs in many cases because of the offensive nature of the discharge and the marital disharmony consequent on vaginismus and dyspareunia.

It now seems clear that *T. vaginalis* is a pathogen and not a harmless inhabitant of the genital tract, though it may be seen occasionally in the absence of clinical signs of infection. Recently, since improved laboratory methods of demonstrating the organism have made diagnosis easier, the protozoon has been shown to be present in the male genito-urinary tract with increasing frequency. Whittington (1957), using cultural techniques, showed the organism to be present in 15.3% of 325 men with non-gonococcal urethritis, and in 8 (33%) of 24 symptomless male consorts of women with chronic trichomonal vaginitis. In a group of 30 husbands of women with chronic trichomonal vaginitis we found that 18 (60%) harboured the organism, most commonly in the prostate (Watt and Jennison, 1960). Male trichomoniasis is in many cases completely silent and may represent a carrier state.

Treatment of human trichomoniasis has until now been very unsatisfactory and at best could often be only palliative. Local pessaries of various kinds in the female produced symptomatic relief in a proportion of cases, but the incidence of recurrence was always high and the incidence of chemical vaginitis by no means negligible. Treatment of the male, especially if a prostatic focus

was present, in many instances presented an insuperable problem, though, as in the case of the female, spontaneous remissions apparently occurred. Among the reasons suggested for failure of local treatment in the female, the existence of a focus of infection elsewhere than in the vagina and repeated reinfestation by male consorts are most likely. The organism has been demonstrated in the urinary tract by Kean (1955) and Whittington (1957), and has been seen on a number of occasions in this hospital. Recurrent vaginitis in virgins, and women who, for one reason or another, are not indulging in coitus, is a well-known entity, so that, though both factors may play a part, extravaginal foci of infection are probably the most important single cause of failure of treatment. The ideal treatment, therefore, is obviously one which is administered systemically, and which can, if necessary, be given to both partners simultaneously.

Various systemic drugs have been used in the treatment of human trichomoniasis but have been abandoned as useless. The most recent of these was acinitrazole (2-acetylamino-5-nitrothiazole), which was considered by Plentl *et al.* (1956) to be effective; but their findings have not been confirmed (Catterall and Nicol, 1957; Willcox, 1957; Jennison, 1957; Dunlop, *et al.*, 1958).

A new derivative of imidazole, metronidazole (1-β-hydroxyethyl-2-methyl-5-nitroimidazole; "flagyl"), was studied by Cosar and Julou (1959) in France, and its antitrichomonal activity and toxicity in both experimental animals and humans have been reported by Durel *et al.* (1960). The original investigations showed definite antitrichomonal activity both *in vitro* and *in vivo*, and significant levels of the drug were found in the blood and urine after ingestion. No severe toxic effects were noted.

Durel *et al.* (1960) report the successful treatment of all of 13 males with urethritis due to *T. vaginalis*. They were given 500 mg. of the drug by mouth in two equal doses daily for 10 days; one patient failed to respond but was cured after a further identical course of treatment. The period of observation varied from 1 to 12 months. Six women were treated with a similar oral course, 21 were treated orally and with vaginal tablets of 500 mg. daily, and four were treated with the drug locally only. One failure (16.6%) occurred in the first group, four failures (19%) in the second group, and one (25%) in the group with local treatment only. The length of the observation period is not recorded.

Present Investigation

In an attempt to determine the clinical efficacy of metronidazole a trial was arranged in St. Mary's Hospital for Women, Manchester, where there exists a special clinic for the treatment of non-specific vaginal infections. Patients are referred to this clinic through the co-operation of the consultant staff, and the investigations and treatment are carried out by the venereologist. It should be pointed out that this clinic is entirely separate from the venereal disease clinic.

Fifty consecutive patients suffering from vaginitis due to *T. vaginalis* were included in the trial (48 white and 2 coloured). Their ages ranged from 17 to 58 years. All were complaining of offensive vaginal discharge of varying duration, some with irritation and others with dyspareunia as a symptom. Before inclusion all patients were shown, by examination of vaginal secretion by direct phase-contrast microscopy, to harbour *T. vaginalis*. Table I shows the duration of symptoms. Since many of the patients were attending the clinic before the commencement of the trial, a high proportion had had symptoms for more than one year (64%) and had had previous ineffective local treatment (66%). One patient was known to have had treatment intermittently for 13 years.

TABLE I.—*Duration of Symptoms in 50 Patients*

	Duration of Symptoms (Months)				Previous Local Treatment
	-3	-6	-12	>12	
Number ..	8	6	4	32	33
Percentage ..	16	12	8	64	66

Monilial infection, atrophic vaginitis, condylomata acuminata, and various gynaecological abnormalities were noted in some patients. One patient was approximately six weeks pregnant at the time of treatment. One suffered from chronic bronchitis and asthma, one from bronchiectasis, one had an active duodenal ulcer, and one was under treatment for mild thyrotoxicosis. Multiple skin sensitivity to antibiotics, sulphonamides, and various pessaries was recorded in one patient, sensitivity to penicillin in another, and sensitivity to acetarsol in two.

Durel *et al.* (1960) favoured combined local and systemic use of metronidazole. In the present series the drug was given by mouth only, 200 mg. t.d.s. for one week. Patients were not advised to avoid coitus.

In the earlier stages of the trial, in an attempt to preclude the possibility of error in assessing symptomatic or clinical improvement, inactive tablets were issued to unselected patients by the hospital pharmacist. He alone knew which patients had the active drug. This was abandoned after 30 patients had been treated, six with inactive tablets. In each of the six cases the lack of clinical response was immediately apparent, and was confirmed by laboratory examination.

Results of Treatment

All patients were asked to report for observation at the end of the first week of treatment, then at weekly intervals, and then at longer intervals when the response to treatment was satisfactory. An arbitrary period of three months' post-treatment observation was fixed as being adequate to assess cure. At each visit a clinical examination was made and specimens of vaginal secretion were obtained by pipette. Specimens were examined immediately by phase-contrast microscopy. All specimens negative by direct examination were inoculated into the medium described by Stenton (1957) and incubated for three days. Patients were regarded as cured only if both direct and cultural examinations were negative.

On examination at the end of treatment and subsequently, 44 patients (88%) showed no clinical or laboratory evidence of infection. The length of observation after treatment is shown in Table II. More than half (56.8%) have completed three months' observation

TABLE II.—*Length of Observation in 44 Cases Treated Successfully*

	Post-treatment Week											
	12+	11	10	9	8	7	6	5	4	3	2	1
Number	25	1	0	1	2	1	3	4	2	4	0	1
Cumulative %	56·8	59	59	61·3	65·9	68·1	75·9	84	88·6	97·7	97·7	100

and have been discharged, and 84% have been observed for more than one month. The average number of post-treatment examinations was four per patient.

In the successful cases symptomatic improvement was apparent during the first few days of treatment, the most notable feature being the rapid relief of irritation. The first post-treatment examination usually showed improvement in the vaginitis, most pronounced in relatively acute vulvovaginitis of recent onset. Vaginal tenderness and vaginismus resolved rapidly in most instances, as, in the absence of complicating factors, did vaginal discharge of recent origin. Patients who had more chronic infections showed improvement over a number of weeks, with gradual lessening of vaginal discharge and slow return to normal of the vaginal wall. In three out of four patients with cervical erosion healing took place coincident with the subsidence of other signs. Four patients with atrophic vaginitis, in addition to trichomonal infection, were made much more comfortable after the disappearance of the flagellate, but the atrophic vaginitis persisted. Coincident monilial infection in six patients and condylomata acuminata in two were unaffected by treatment.

One striking effect of treatment was noticed in the mental attitude of patients who responded. Many had become depressed at the failure of previous treatment, some who had taken part in previous abortive clinical trials approached yet another with considerable scepticism, yet within a week their attitude changed and depression and anxiety lessened with continuing relief of symptoms.

At the first post-treatment examination *T. vaginalis* was not found in the specimens obtained from any patient who responded to treatment. At the time of this examination, in most cases the course of treatment had just finished and presumably active serum levels of the drug were still present. At subsequent examinations *T. vaginalis* was not recovered from any of this group.

Failure to Respond to Initial Course

Six patients did not respond to the initial course of treatment. Table III summarizes the results of the laboratory examinations in these. Five were white and one was coloured. Four were married and two were single but cohabiting.

TABLE III.—*Results of Laboratory Examination in Patients not Responding to Treatment. (Positive Implies T. Vaginalis seen or cultured)*

Case	Marital Status	Age	Duration of Symptoms	Initial Treatment (600 mg. Daily)				Re-treatment (1,200 mg. Daily)			
				Post-treatment Week							
				1	2	3	4	1	2	3	4
1	M	39	3 months	Neg.	Pos.			Neg.		Neg.	Neg.
27	M	34	5 years	Neg.		Neg.	Pos.	Neg.		Neg.	Neg.
28	M	27	2 months	Pos.							
35	M	28	6 ,,	Pos.				Neg.		Neg.	
39	S	24	6 ,,		Neg.		Pos.				
46	S	42	6 ,,		Pos.						

Case 1.—Married. Vaginitis for three months. Clinical improvement on first post-treatment visit was maintained on second visit, but direct examination revealed *T. vaginalis*. Admitted coitus since treatment. Husband clinically, and on culture, free from infection. Patient re-treated with similar course. Clinical improvement maintained, but at first post-treatment visit again showed *T. vaginalis* on direct examination. Probable treatment failure. Re-treated with 1,200 mg. daily, and has apparently responded. Husband not treated.

Case 27.—Married. Chronic relapsing vaginitis under treatment for five years. Stated no improvement at first post-treatment visit and clinically still showed vaginitis though *T. vaginalis* not found. Examined two and three weeks later. Still complained of discharge and irritation, and clinically unchanged. *T. vaginalis* not found on second examination. Direct microscopy on third examination was negative, but culture showed *T. vaginalis*. Denied coitus. Husband examined on previous occasion and found negative. Probable treatment failure. Has apparently responded to higher dosage and is clinically improved. Husband not treated.

Case 28.—Married. Vaginitis with *T. vaginalis* and candida. Complained of increase of irritation whilst on treatment. Clinically not improved on first post-treatment visit, and direct examination showed *T. vaginalis*. Denied coitus. Husband not examined. Probable treatment failure. Unable to tolerate higher dosage.

Case 35.—Married. Vaginitis for six months. Stated no improvement on first post-treatment visit and still showed vaginitis. Direct examination revealed *T. vaginalis*. Defaulted and returned after one month with acute trichomonal vaginitis. Admitted coitus on this occasion. Husband not examined. Probable treatment failure. Has apparently responded to higher dosage. Husband not treated.

Case 39.—Single. Cohabiting. Delivered of child six months previously. First post-treatment examination showed clinical improvement and no *T. vaginalis*. Second post-treatment visit after two weeks showed no vaginitis, but direct examination revealed *T. vaginalis*. Defaulted. No further information available. Reinfection cannot be excluded.

Case 46.—Single. Jamaican. Cohabiting. First post-treatment visit after two weeks showed clinical improvement. Direct examination negative but culture grew *T. vaginalis*. Defaulted. No further information available. Reinfection cannot be excluded.

Of the six patients who failed to respond to the initial course of treatment, three showed clinical improvement at the first post-treatment examination. This was maintained on subsequent examination, though direct microscopy in two cases and culture in one case revealed *T. vaginalis*. Three patients failed to show clinical response to treatment on the first visit and two showed *T. vaginalis* on direct examination. One was followed for four weeks without clinical improvement, culture finally demonstrating the organism when direct examination was negative. Three of these patients have apparently responded to increased dosage.

Side-effects of Treatment

All 50 patients reported for at least one post-treatment examination. The possible side-effects encountered by those treated with a daily dosage of 600 mg. and by four who were re-treated with 1,200 mg. are summarized in Table IV. No side-effects were reported by 39 (78%) patients treated with 600 mg. daily, but all four on the higher dosage complained, one having to stop treatment

TABLE IV.—*Side-effects of Treatment*

Side-effects	Total Daily Dose 600 mg. (50 Patients)		Total Daily Dose 1,200 mg. (4 Patients*)	
	No.	%	No.	%
Bad taste	1	2	—	
Anorexia	2	4	1	
Flatulence	3	6	—	
Nausea	2	4	—	
,, +Dizziness	1	2	2	
,, +Vomiting	—	—	1	
Headache	2	4	2	
Agitation	—	—	2	
Total No. of patients	11	22	4	100

* All patients reported multiple symptoms.

because of vomiting. Most of the side-effects were minor and associated with the gastro-intestinal tract, but two patients on the lower dosage reported headache and two on the higher dosage noted headache in association with dizziness and agitation and with dizziness and nausea. Dizziness of severe degree was mentioned by one patient on the lower dosage and by one on the higher dosage—neither had nystagmus, but one showed definite Rombergism. Two patients on the higher dosage reported agitation and a feeling of tension. The patient who was pregnant reported nausea but no vomiting. All side-effects ceased on stopping the drug. None of the patients who suffered from other ailments noted any worsening of their condition, and no evidence of skin sensitivity was observed in any patient.

Discussion

A long observation period is necessary before claims regarding the efficacy of any antitrichomonal agent are substantiated. In the present series of 50 consecutive patients treated with metronidazole, 44 (88%) have responded to treatment, and 25 (56.8%) of these have remained free from infection on clinical and laboratory examination for three months or longer, 29 (65.9%) for two months, and 39 (88.6%) for one month. This indicates that the drug shows considerable promise in the chemotherapy of trichomonal infections. Clinical response appeared to be dramatic, especially in acute vulvovaginitis of recent onset. Irritation, vaginismus, and inflammation disappeared within a week. Symptomatic response in chronic cases was equally dramatic, especially the relief of irritation, but clinical examination of such cases revealed a slow process of resolution. Dyspareunia was relieved in three out of four patients in whom it was a presenting symptom.

Reactions to treatment occurred in 11 patients (22%) treated with 600 mg. daily, and in all four patients treated with 1,200 mg. daily. The side-effects were not incapacitating in most cases, and only one patient, on the higher dosage, was unable to continue treatment. Durel *et al.* (1960) found no evidence of damage to the haemopoietic system, and in 10 patients we have examined after treatment the red-cell, white-cell, and platelet counts were normal.

Treatment failed in 6 (12%) patients. Three have been re-treated with the higher dosage (1,200 mg. daily) and have apparently responded, though the observation period is as yet too short to draw final conclusions.

Failure of treatment may be due to insensitivity of certain strains of *T. vaginalis*, to poor absorption of the drug, or to reinfection.

Fourteen strains of *T. vaginalis* have been tested for sensitivity to metronidazole by culturing in media containing the drug and incubating for three days. This method differs from that of Bushby and Copp (1955), but we believe our technique to represent more closely the conditions *in vivo*. With our technique the majority (nine) of the strains tested were killed by dilutions of 1 in 4 million or greater. Of the five strains growing in concentrations of 1 in 2 million or stronger, three came from patients who had not responded to the initial course of treatment.

The concentration of the drug in patients' serum and urine is being estimated, but it is as yet too early to draw conclusions on the relationship of serum levels and resistance to treatment.

Both these aspects of the investigation of metronidazole will be reported in full later.

Although patients were not advised to avoid coitus, only two have possibly been reinfected during the period of observation. In this series, and within the limits imposed by the period of observation, reinfection from sexual partners would not appear to be a common cause of failure of treatment. In fact, reinfection would seem to be most unlikely in those patients who still showed *T. vaginalis* at the first post-treatment visit—that is, just having completed treatment—because such patients, if they absorb the drug, should still have a trichomonacidal level in the blood which would act prophylactically. Reinfection cannot, however, be excluded in any patient who failed to respond to treatment, unless there is proof of inadequate absorption or the presence of a resistant strain of *T. vaginalis*.

In many patients who responded to treatment, especially those with chronic vaginitis, marked and understandable psychological benefit was very apparent.

Summary

A new derivative of imidazole, metronidazole (1-β-hydroxyethyl-2-methyl-5-nitroimidazole ; " flagyl "), was investigated in the treatment of trichomonal vaginitis in 50 consecutive patients. Dosage was 600 mg. given by mouth daily for seven days. No local treatment was used. Test of cure included laboratory examination by direct and cultural methods.

Of 44 (88%) women responding to the initial course of treatment, 25 (56.8%) have remained free from infection on clinical and laboratory examination for three months or longer, 29 (65.9%) for two months, and 39 (88.6%) for one month. Six patients (12%) were regarded as treatment failures or as reinfections ; three of these have apparently responded to re-treatment with 1,200 mg. daily for one week.

Side-effects occurred in 11 patients (22%) treated with the lower dose and in all four patients on the higher dose. One patient could not tolerate the drug in higher dosage.

In this series reinfection would not appear to be a common cause of failure of treatment during the period the patients were under observation. Such failure may possibly be due to the existence of relatively less sensitive strains of *T. vaginalis* or to inadequate absorption of the drug.

This preliminary investigation indicates that metronidazole appears to be an effective trichomonacide when taken orally. Local treatment is apparently unnecessary.

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SYSTEMIC TREATMENT OF TRICHOMONAS VAGINALIS INFESTATION IN WOMEN

A PRELIMINARY REPORT

BY

ELISABETH REES, M.D.

Department of Venereal Diseases, Liverpool Royal Infirmary

The combined oral and systemic treatment of *Trichomonas vaginalis* infestation in women by metronidazole 1-β-hydroxyethyl-2-methyl-5-nitroimidazole (RP 8823; "flagyl"), a derivative of nitroimidazole, has been reported by Durel *et al.* (1959) and Sylvestre *et al.* (1959). At Liverpool Royal Infirmary a clinical trial of this preparation administered systemically without any concurrent local therapy was instigated in December, 1959. The preliminary results are reported.

The patients taking part were women who attended the female venereal disease department either at the special clinic or at the "non-specific" clinic which is held in the gynaecological out-patient department. Patients are referred to the former by their general practitioners or other hospital departments, or attend as contacts of male cases of gonorrhoea or on their own accord. Patients are referred to the latter, as contacts, by male cases of non-specific urethritis who are attending male venereal disease clinics.

In view of the variability in demonstrating trichomonads on examination of wet preparations in the carrier type of case, treatment was limited initially to cases showing an acute infestation, in order that an immediate clinical assessment could be made. In the first four cases treated the clinical and symptomatic response was prompt. Thereafter, all those who presented and in whom trichomonads were demonstrated in wet preparations received metronidazole. Culture methods of diagnosis were not available in the clinic or the hospital laboratory, but permission was given by Professor T. N. A. Jeffcoate for cultures to be supplied and examined by his department. These were used in the follow-up of all cases treated with metronidazole. The culture medium used was the Feinberg–Whittington liquid liver medium (Feinberg and Whittington, 1957). As the vaginal discharge became thick and often scanty after treatment, the specimen was collected on a swab stick, the end of which was broken off into the bottle containing the medium. This was incubated within five minutes of inoculation and examined after 24 hours. Negative cultures were re-examined after 72 hours. Centrifuging was not carried out. Trichomonads were reported present 1+, 2++, or 3+++, according to the number present. *Candida albicans* was reported when found. Diagnosis was by microscopical examination of fresh preparations in normal saline in the clinic within fifteen minutes of taking.

Clinically, cases were recorded as acute, subacute, or carrier according to the clinical signs present at the time of diagnosis. A full clinical examination was recorded at each attendance by the same clinician, except on a few occasions during absence on leave. In cases in which gonorrhoea was diagnosed, treatment for *T. vaginalis* infestation was withheld for one week after completion of treatment for gonorrhoea in order that a more accurate clinical assessment could be made.

Patients were asked to attend for observation weekly for four weeks, and after the next two menstrual periods. Difficulty was experienced in persuading patients to continue observation when they were symptom-free and believed themselves cured.

The number of patients who received metronidazole was 48, of whom 9 failed to return for any follow-up tests. Of the 39 patients who did attend for observation 15 had gonorrhoea. Two of these patients received metronidazole before the diagnosis of gonorrhoea was made, as gonococci were demonstrated only in the second series of tests. 11 patients were married, 2 were married but separated, and 26 were single. All admitted sexual intercourse except one girl aged 16 who was not virgo intacta. Metronidazole was prescribed in a dosage of 200 mg. three times a day for seven days. Initially, no directions regarding pre- or post-prandial administration were given, but after complaints of nausea in some patients the directions were changed to three times a day after meals. So far as can be judged within the limits of the numbers treated, this led to a diminution in the proportion of patients complaining of gastric symptoms.

Except in those who had gonorrhoea, married women and women with a single regular consort were not asked to abstain from sexual intercourse, it being thought that a more reliable method of ensuring against reinfection was to treat the male partner concurrently, if possible. Metronidazole in similar dosage was given to the male partners who were attending the male venereal disease clinics, irrespective of whether trichomonads were demonstrated in them. Women, whose husbands or regular consorts were not attending a clinic, were given metronidazole for their partners to take concurrently. In all except one case the men were said to have co-operated.

Seven of the 39 patients were resident in approved schools; three of these absconded early in their period of observation.

Clinical Assessment at Time of Diagnosis

Acute infestation was recorded when the clinical signs of vulvitis, congestion of the urethra usually associated with purulent discharge, copious thin purulent vaginal discharge, and punctate erythema of the vaginal walls were present.

Subacute infestation was recorded when there was no vulvitis, little or no congestion of the urethra, mucoid or absent urethral discharge, moderate to much thin mucoid or muco-purulent discharge, and no punctate erythema of the vaginal walls.

Carrier type of infestation was recorded in the absence of any clinical signs of *T. vaginalis*.

The incidence of these clinical groups in the 39 cases was: acute, 14; subacute, 19; carrier, 6.

Results of Treatment

A: Acute Cases

Clinical Results.—The response to treatment was prompt and identical in the majority of cases. By the seventh day of treatment the vulva was dry, purulent urethral discharge had changed to mucoid or was absent, the vagina contained thickish mucoid discharge slightly excessive or normal in quantity, and residual

congestion of the vaginal walls was present but gradually decreased and disappeared during the ensuing week. Detailed results are given in Table I. The two cases in which there was no response to treatment were Nos. 4 and 6. Case 4 was that of a 16-year-old girl who finally admitted taking the tablets only

TABLE I.—*Clinical Response Seven Days After One Course of Metronidazole*

No. of Cases	Clinically Normal	No Response	Not Recorded
14	11	2	1

morning and evening when she remembered. A second course, given a week after the first course, was supervised by the mother and resulted in a complete clinical and symptomatic response. Case 6 was that of a 15-stone woman who denied irregular treatment. It was thought possible that the failure might be associated with her weight. However, a second identical course prescribed a week after the first course resulted in a prompt clinical and symptomatic response. The fact that this patient complained of nausea and vomited twice during the second course, while apparently suffering no toxic symptoms during the first course, suggests the possibility that she did not take the latter.

TABLE II.—*Presenting Symptoms*

T.V. and Gonorrhoea				T.V. Uncomplicated			
No. of Cases	Disch.	Disch. and Irritation	Not Rec.	No. of Cases	Disch.	Disch. and Irritation	Not Rec.
3	2	—	1	11	8	3	—

Not rec. = Not recorded.

TABLE III.—*Symptomatic Response Seven Days After One Course of Metronidazole*

No. of Cases	Symptom-free	Much Improved	No Response	Not Recorded
14	9	2	2	1

TABLE IV.—*Laboratory Results*

Case No.		Weeks from Beginning of Treatment							
		1	2	3	4	6	8	12	16
1	S.		−	−	−		−	−	
	C.	−	+++	−	+		+	−	
2	S.		−						
	C.	−	+						
3	S.	−							
	C.	++							
4	S.	−	−	−		−	−		
	C.	+	+++	+		−	−		
5	S.	−	−	−	−				
	C.	−	−	−	−				
6	S.		+	+	−				
	C.		+++	+	−				
7	S.		−	−	−	−	−	−	−
	C.		−	−	−	+	−	−	−
8	S.	−	−		−				−
	C.	+	+		+				−
9	S.							−	
	C.							−	
10	S.	−							
	C.	−							
11	S.	−		−	−		−		
	C.	−		−	−		−		
12	S.	−		−		−			
	C.	−		−		−			
13	S.		−	−			−		
	C.		−	−			−		
14	S.		−	−					
	C.		−	−					

S. = wet smear. C. = culture. − = No trichomonads present. +++ = Numerous trichomonads present. + = A few trichomonads present.

Symptomatic Results.—The majority of patients seen at seven days were symptom-free (Tables II and III). One experienced and intelligent patient who had had three previous attacks of acute infestation stated that the "drying-up" began on the second day of treatment.

No response was recorded in Cases 4 and 6, described above. Both responded to a second course of treatment, one being symptom-free and one having a slight residual discharge.

Laboratory Results.—These results are tabulated in Table IV.

No clinical or symptomatic relapse was observed throughout the periods of observation recorded. No history of sexual intercourse with an untreated partner was obtained.

B: Subacute Cases

Clinical Results.—Clinically, results were less dramatic than in acute infestations. Mucoid urethral discharge usually cleared unless there was associated prolapse of the anterior vaginal wall, and mucopurulent

TABLE V.—*Clinical Response Seven Days After One Course of Metronidazole*

No. of Cases	Clinically Normal	Much Improved	No Response	Not Recorded
19	8	7	2	2

TABLE VI.—*Correlation Between Symptoms and Clinical Signs in Eight Patients Judged to be Clinically Much Improved But Not Clinical Normal*

No. of Patients	Asymptomatic 7 Days After Treatment	Asymptomatic Before Treatment	Symptomatically Much Improved	Not Recorded
8	3	2	2	

TABLE VII.—*Presenting Symptoms*

T.V. and Gonorrhoea					T.V. Uncomplicated			
No. of Cases	Disch.	Disch. and Irritation	Lower Abdominal Pain	Symptom-free	No. of Cases	Disch.	Disch. and Irritation	Symptom-free
9	6	1	1	1	10	6	2	2

TABLE VIII.—*Symptomatic Response Seven Days After One Course of Metronidazole*

No. of Cases	Symptom-free	Much Improved	No Response	Not Recorded
19	14	2	—	3

vaginal discharge changed to mucoid in character, becoming thick in most cases and normal in quantity. In a proportion of cases the residual discharge was judged clinically to be in excess of normal, although many of these patients regarded themselves as symptom-free (Tables V and VI).

Symptomatic Results.—Most patients were symptom-free at the end of the course of treatment (Tables VII and VIII). Two patients who were asymptomatic before treatment noticed a decrease in the amount of discharge, which they had previously regarded as normal.

Laboratory Results.—These results are tabulated in Table IX.

Case 16 defaulted for 12 weeks, and on her return had relapsed clinically and symptomatically. She admitted sexual intercourse, and gonococci and *T.*

TABLE IX.—*Laboratory Results (Subacute Cases)*

Case No.		Weeks from Start of Treatment								
		1	2	3	4	6	8	12	16	20
15	S.	−	−		−	−	−	−	−	−
	C.					+	−	−	−	−
16	S.	−	−					+		
	C.							+		
17	S.	−		−	−	−	−	−		
	C.	+		+	−	−	−	−		
18	S.		−				−			
	C.		−				−			
19	S.	−	−	−			−		−	
	C.	−	−	−			−		−	
20	S.	−			−		−	−	−	
	C.	+++			+		−	−	+	
21	S.	−	−	−			−			
	C.	+	−	−			−			
22	S.	−	−		−		−	−		
	C.	+	−		−		−	−		
23	S.	−		−						
	C.	++		−						
24	S.	−		−	−	−	−	−		
	C.	+		−	−	−	−	−		
25	S.	−		−	−	−	−			
	C.	++		+	−	−	−			
26	S.		−		−		+	−		
	C.		−		−		−	−		
27	S.	−	−		−	−		−		
	C.	+	−		−	−		−		
28	S.	−	−	−			−			
	C.	−	−	−			++			
29	S.	+		−						
	C.	+++		−						
30	S.	−					−			
	C.	−					−			
31	S.				−		−			
	C.				−		−			
32	S.	−	−							
	C.	−	−							
33	S.	−	−		−					
	C.	−	−		−					

S. = Wet smear. C. = Culture. − = No trichomonads present. +++ = Numerous trichomonads present. + = Few trichomonads present.

vaginalis were demonstrated in her cervical and vaginal secretions respectively. She was judged to be reinfected.

Case 24 reported reappearance of some discharge at six weeks. There was no irritation, but *C. albicans* had been found in a previous test. There were no clinical signs of *C. albicans*, but nystatin was prescribed and the symptoms resolved.

Case 21 reported the presence of some discharge at eight weeks, after being symptom-free from the end of treatment. Clinically very little mucoid discharge was found.

Case 28 presented with a moderate amount of thin mucoid vaginal discharge with gas bubbles. She complained only of vague lower abdominal pain. No clinical response to treatment was observed throughout the period of observation. Laboratory tests were negative after treatment (Table IX), but a positive culture was obtained in the eighth week of observation. This patient is resident in an approved school.

In no other case was clinical or symptomatic relapse observed.

TABLE X.—*Laboratory Results (Carriers)*

Case No.		Weeks from Start of Treatment						
		1	2	3	4	6	8	12
34	S.	−						
	C.	+						
35	S.	−		−	−	−		−
	C.	+		−	−	+		−
36	S.		−			−		−
	C.		−			−		−
37	S.	−	−		−			
	C.	−	−		−			
38	S.		−					
	C.		−					
39	S.	−		−		+	−	
	C.	−		−		−	++	

S. = Smear. C. = Culture. − = No trichomonads present. ++ = Many trichomonads present. + = Few trichomonads present.

C: Carrier Cases

All six cases had no clinical signs of *T. vaginalis* infestation, and were asymptomatic. They attended for the following reasons: contacts of cases of non-specific urethritis, 2; contacts of cases of gonorrhoea, 3; routine tests in approved school, 1.

Laboratory Results.—These results are tabulated in Table X.

Case 39 was that of a single girl who in the sixth week of observation admitted sexual intercourse with an untreated male consort who had used a condom.

Case 35 was a contact of her husband, who had non-specific urethritis. Both were treated with metronidazole. No clinical signs of symptoms accompanied the positive laboratory tests in either case.

Toxic Reactions

Toxic reactions were reported by five patients. One complained of a bitter taste in the mouth, two complained of slight nausea, one complained of marked nausea resulting in vomiting on two occasions, and one complained of irritation of the skin of the forearms with "red scaling patches" which appeared on the second day of treatment. This patient continued treatment and the rash started to fade. Examination on the seventh day revealed fading irregular squamous papules on both forearms.

Candida Albicans

C. albicans grows luxuriantly in the Feinberg–Whittington medium. Its presence was reported in 9 of the 39 cases at some time during the follow-up period. No irritation was reported by any of the nine patients, one complained of slight discharge after being symptom-free for five weeks. A request was made to the department of obstetrics and gynaecology for an estimated comparison of the incidence of *C. albicans* in specimens from the special clinic and those from the gynaecological clinic where cultures were being use for diagnostic purposes and where no metronidazole had been given. No significant difference was reported. It was therefore concluded that metronidazole did not encourage or suppress the growth of *C. albicans* and that the culture medium merely supported the growth of a normal inhabitant.

Treated Partners

10 of the 39 patients attended as contacts of their husbands or consorts, who had non-specific urethritis. Of five males who attended the Seamen's Dispensary, *T. vaginalis* was demonstrated in three after recurrent relapse resulted in the attendance of the wife at the "non-specific" clinic and the diagnosis in her of *T. vaginalis* infestation. Wet smears of centrifuged urine were positive in two cases and the prostatic bead in one. Culture methods of diagnosis were not available. Metronidazole was given to all husbands and wives. Two of the three men remain symptom-free three months and six weeks respectively after treatment. One has defaulted.

All five males who attended the Liverpool Royal Infirmary clinical were given metronidazole after their

treatment for non-specific urethritis. Urine centrifuged on one occasion revealed no trichomonads in wet smears. Culture methods of diagnosis were not available.

In addition, on epidemiological grounds, treatment for husbands who were symptom-free and not attending a male clinic was given to five wives. The husbands were said to have co-operated.

Summary of Results of Treatment

The clinical results of treatment were recorded within seven days of the end of treatment in 30 of the 33 patients in whom clinical signs of *T. vaginalis* were present (13 acute and 17 subacute infestations). The response in two patients (Cases 4 and 6) is after the second course of treatment (Table XI).

TABLE XI.—*Total Clinical Results After Treatment in* 30 *Patients Showing Clinical Signs of T. vaginalis Infestation*

	Clinically Normal	Much Improved	No Response
Number	20	8	2
Percentage ..	66·7	26·7	6·6

The symptomatic results were recorded within seven days of the end of treatment in 26 of the 30 patients who had symptoms (13 acute, 13 subacute). The response in two patients (Cases 4 and 6) followed the second course of treatment (Table XII).

TABLE XII.—*Total Symptomatic Results After Treatment in* 26 *Patients With Symptoms*

	Symptom-free	Much Improved	No Response
No. of patients ..	21	5	0
Percentage ..	80·8	19·2	0

The difference between the clinical and symptomatic results suggests that the clinical assessment erred on the cautious side. In all except two subacute cases (Cases 17 and 28), who regarded themselves as symptom-free and whose laboratory results were satisfactory, the clinical response to treatment was most pronounced, the residual symptoms or signs when present being of a minor character and possibly due to another cause.

Laboratory results after treatment showed some difference in pattern between wet smears and cultures (Table XIII).

TABLE XIII.—*Laboratory Results at First Test After Treatment in* 39 *Cases*

	Wet Smears		Cultures	
	Negative	Positive	Negative	Positive
Number	38	1	22	17
Percentage ..	97·4	2·6	56·4	43·6

In four cases, which were tested at four days, wet smears were already negative though cultures were positive +++ in three cases. It was thought that metronidazole immobilized the trichomonads, making them difficult to recognize microscopically.

No association between positive culture results and the clinical type of infestation was found. The 17 positive cultures were distributed as follows: acute, 6; subacute, 9; carrier, 2. No difference between the clinical and symptomatic response of patients with positive cultures and those with negative cultures was observed.

Cultures usually became negative in the second or third week of observation (Tables VII, IX, X). In 10 cases a positive culture was reported in four weeks or later. In only one case (Case 16) was this associated with clinical or symptomatic relapse and a positive wet smear. This patient was judged to be reinfected.

Conclusions

Metronidazole administered systemically in the absence of any local therapy is a most effective remedy in the treatment of *T. vaginalis* infestation in the female. Continued observation of treated cases is necessary to assess its long-term value, particularly in cases in which positive culture tests after treatment have been reported.

The possible hazards associated with its use should be recognized. The high incidence of *T. vaginalis* infestation in women suffering from gonorrhoea (in 1958, 66% in female patients attending Liverpool Royal Infirmary), together with the asymptomatic nature of gonococcal infections in approximately half the female patients seen in venereal disease clinics, demonstrates the danger present in its indiscriminate use in promiscuous women, or, indeed, in any woman who has sexual intercourse with a partner who may be promiscuous. In the absence of any bacteriological investigation the rapid disappearance of discharge after treatment with metronidazole will undoubtedly result in the delayed diagnosis or non-diagnosis of gonorrhoea in many women harbouring both gonococci and *T. vaginalis*.

I am indebted to Professor T. N. A. Jeffcoate, Professor of Obstetrics and Gynaecology in the University of Liverpool, for the provision and examination of cultures by his department; to Mr. H. H. Francis, Senior Lecturer in Obstetrics and Gynaecology, for his co-operation; and to Mrs. P. M. Thomas, senior laboratory technician in the department of obstetrics and gynaecology, who reported on the cultures.

I would like to thank Dr. E. E. Prebble and Dr. C. D. Alergant, at the Venereal Disease Department, Liverpool Royal Infirmary, and Dr. F. Lanceley, Dr. J. L. Fluker, and Dr. A. S. W. Egerton, at the Seamen's Dispensary, for their co-operation in treating male contacts at my request and for access to their records. I am also grateful to Miss E. R. Smith for her welfare work and secretarial assistance throughout the trial.

The supplies of metronidazole were provided by Messrs. May and Baker Ltd.

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The National Association for Mental Health has recently published *Child Guidance at Home and Abroad* (price 3s. 6d.), the proceedings of the Sixteenth Inter-Clinic Conference for Staffs of Child Guidance Clinics held on April 22 and 23. Papers were read on: the efficacy of child-guidance clinics; some aspects of child guidance in Belgium; questions facing mental health workers with children in Italy; and the child psychiatric scene in Scotland and Israel—a study in contrast.

TREATMENT OF TRICHOMONIASIS WITH METRONIDAZOLE

BY

MARY MOFFETT, M.B., Ch.B., D.P.H.
Special Clinic, Govan Town Hall, Glasgow

AND

M. ISABEL McGILL, M.B., Ch.B., D.P.H.
Black Street Clinic and Ruchill Hospital, Glasgow

It is generally agreed that vaginitis due to *Trichomonas vaginalis* is easy to treat and difficult to cure. Substances for local use have so far offered only a limited prospect of eliminating the organism ; symptoms are relieved but relapse is frequent. The solution of this problem seemed to be a preparation which would be effective systemically, but the results with "trichomycin" and acinitrazole were disappointing. The continued search for a more effective substance led to experimental work on metronidazole (1-β-hydroxyethyl-2-methyl-5-nitroimidazole ; "flagyl" or 8823 R.P.) by Cosar and Julou (1959), and the clinical study of Durel, Roiron, Siboulet, and Borel (1960) has opened up a new line of investigation.

Present Investigation

The patients in this series were women who were attending out-patient clinics for the treatment of venereal diseases. In the course of a routine investigation they were all examined for the presence of the gonococcus and of *T. vaginalis*. Specimens from the urethra and vagina were conveyed to the Glasgow Public Health Laboratory in Stuart's transport medium, which preserves the vitality of the trichomonads, although it was produced primarily to keep the gonococcus alive in transit. At the laboratory a wet film was examined, and if trichomonads were not found a culture was made.

The drug was given to those patients who, by film or culture, were found to harbour the protozoon. The degree of infection varied from heavy, with profuse discharge, to light, with few parasites and only slightly increased secretion. No selection was made, other than exclusion from the trial of those women who were assessed as almost certain to default. Even with this reservation 5 out of the 42 patients to whom the drug was given failed to return. Four patients in the series were post-menopausal, six were pregnant, and three suffered from a concurrent vaginal mycosis.

The first 14 patients were treated with one 200-mg. tablet orally thrice daily for 10 days, and one 0.5-g. vaginal pessary each night during that period. The next 24 patients were given the same oral dosage but no local treatment. The most recently treated cases, four to date, were given the same daily dosage, but for seven days only.

Of the 42 patients treated, 26 had a concurrent trichomonal and gonococcal infection, and these women were instructed to attend for the surveillance usual in the latter disease. Routine tests of cure were made at the same time for the trichomonal infection: it was hoped to persuade *all* patients to attend for these tests after three successive menstrual periods, but this proved to be a more perfectionist pattern than they were disposed to follow. Most of them did attend during the first two weeks after treatment, and after the first period ; some returned after the second period, and some completed the full three months. Tests of cure consisted in every case of direct examination of wet films and cultures from urethra and cervix, the culture medium being that advocated by Feinberg and Whittington (1957).

Table I shows the extent to which it was possible to assess the cure rate, and the duration of surveillance for each case.

TABLE I.—*Results of Tests of Cure*

Result	Duration of Surveillance after Treatment						Total No. of Patients
	4 Days	1 Week	2 Weeks	1 Month	2 Months	3 Months	
Successful ..	2	2	1	9	12	14	40
Failed ..	0	0	0	2	0	0	2

Where it was possible to examine the patients on the third day after the start of treatment it was found that the trichomonads in all these cases had disappeared and symptoms had subsided. This was not our experience with an earlier preparation said to be active by mouth, but the problem in the past has not been the immediate control of trichomonal vaginitis but its permanent elimination. Metronidazole appeared to be effective in pregnant women and without additional hazard ; it was also successful in three out of the four post-menopausal patients. The presence of a cervical erosion, which formerly seemed to make the cure of trichomonal vaginitis even more difficult, did not interfere with the response to metronidazole.

In three patients found to harbour *Candida albicans* the presence of this infection had not been apparent before metronidazole was given ; the effect of the drug was to play up the mycosis. One of these patients suffered so severely from pruritus vulvae that she stopped taking the drug after three days, but, in spite of this truncated dosage, trichomonads did not reappear ; in the second patient symptoms were of moderate degree and the full course of the drug was given ; the third had no symptoms due to candida.

The results of treatment are shown in Table II.

TABLE II.—*Results with Different Schedules of Treatment*

Result	Metronidazole		
	200 mg. Orally t.i.d. and 0·5-g. Pessary Daily for 10 Days	200 mg. Orally t.i.d.	
		For 10 Days	For 7 Days
Cured ..	13	24	3
Relapsed ..	1	0	1

Patients Who Failed to Respond

Case 1.—This patient, aged 50, was treated by oral and vaginal routes for 10 days. Trichomonads were found after the first and second months, and she was again treated systemically for 10 days. Trichomonal vaginitis was again present. This patient must therefore be regarded as resistant to metronidazole.

Case 2.—This patient, aged 19, had a very profuse discharge with numerous trichomonads. She was given seven days' oral treatment and relapsed after the first period. There has not yet been time for re-treatment ; the result shows that a course of treatment lasting seven days was not sufficient for this patient, and suggests that a heavily infected patient may require longer treatment.

A third patient, aged 19, who had oral treatment only for 10 days, had negative tests after one week, two weeks, and after the first period. Trichomonads were found after the second period, but without further treatment tests have

been negative after three subsequent periods. This patient was therefore regarded as cured.

Summary and Conclusions

A series of 42 patients were given metronidazole for trichomoniasis; there were two failures (4.7%). This compares favourably with the results of local treatment and with the results of previous oral preparations. Side-effects were infrequent: only one patient developed nausea of sufficient severity to stop the drug.

Metronidazole has no effect on candida; with the reduction of their rivals, however, candida may be encouraged.

Durel *et al.* concluded that systemic treatment may be an adjunct to local treatment, but our experience suggests that systemic treatment alone is sufficient for vaginal and urinary infections. With the possibility of treating the husband or consort simultaneously a fruitful source of relapse is overcome.

Results have hitherto been such that caution is necessary until findings can be assessed over a longer period, but our evidence in this series seems to justify a more extensive trial of the drug.

We gratefully acknowledge the help and co-operation of Dr. Jean Young, of the Glasgow Public Health Department, in carrying out the laboratory investigations in this trial; also of the laboratory of Falkirk and District Royal Infirmary, especially Mr. W. Bertram, who contributed to this part of the work. We are also grateful to Dr. Robert Forgan for his encouragement and help, and to May & Baker Ltd. for generous supplies of metronidazole.

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PHENMETRAZINE HYDROCHLORIDE IN TREATMENT OF OBESITY

BY

J. H. BRIGGS, M.R.C.P.
Registrar

P. M. NEWLAND, B.Sc.
Senior Dietitian

AND

P. M. F. BISHOP, D.M., F.R.C.P.
Endocrinologist

Department of Endocrinology, Guy's Hospital, London

Phenmetrazine hydrochloride is the approved name of the compound 2-phenyl-3-methyl-tetrahydroxazine hydrochloride, marketed under the trade name of "preludin." It is related to ephedrine and has chemical and pharmacological similarities to amphetamine. In reviewing this pharmacological relationship, Thomä and Wick (1954) infer that drugs of the amphetamine group suppress the appetite by their action on hypothalamic nuclei; according to Natenshon (1956) phenmetrazine has less tendency to raise the blood-pressure or to stimulate the cerebral cortex than amphetamine, the administration of which is sometimes accompanied by such side-effects as insomnia, anxiety, and palpitations.

Anand and Brobeck (1951) have shown that experimentally produced hypothalamic lesions may lead to anorexia or a voracious appetite, according to which nuclei are affected, and that appetite and satiation are opposing sensations that are under hypothalamic control. Berneike (1955) has suggested that the action of phenmetrazine is to induce the feeling of satiation earlier than it would normally occur. Fazekas *et al.* (1958) studied the effect of phenmetrazine and of placebo tablets in a series of adult patients attending a weight-reduction clinic, but these were given an "individualized diet" of unspecified calorie value. Moreover, the results were not standardized for the patients' initial percentage overweight. Rendle-Short (1960) has described the effect of phenmetrazine on the weight of obese children who were on an unrestricted food intake, and showed that the drug was effective in producing a loss of weight in these circumstances.

The object of the present investigation was to study the effect of phenmetrazine given to obese adults on a restricted diet by comparing the effect with that produced by a placebo.

Method and Material

Women between the ages of 20 and 66, and at least 15% overweight (Levine, 1923) but otherwise healthy, who attended the endocrine department for the treatment of obesity, were asked to take part in the trial. Sixty consented to do so, but only 32 completed it, possibly because of a widespread bus strike at that time. Of these 32, 16 were in each group. Of the 28 patients who defaulted, 19 failed to attend after the first visit, and, of these, 12 had been given the active drug. At the first visit an attempt was made by one of us (P. M. N.) to assess the daily calorie intake from the patient's own description of her diet, although this can be a notoriously unreliable procedure.

The patients were divided randomly into two groups irrespective of the degree of obesity and age, and all were instructed to take one tablet three times a day half an hour before meals. One group of patients were given phenmetrazine 25 mg. thrice daily for four weeks, followed by placebo tablets of identical apearance for the next four weeks. The placebo tablets were administered for the first four weeks to the other group, and then these patients were placed on phenmetrazine. The tablets were dispensed by one of us (J. H. B.), who was aware of their nature; the patients were unaware that some of the tablets were inert. No patient received any other drug treatment to suppress appetite during the trial or three months before it started. All patients were given a 1,000-calorie diet sheet and told to carry out the instructions on it or to continue on their present dietary regime if they were consuming less than 1,000 calories.

Each patient was weighed in indoor clothes without shoes on scales the accuracy of which was checked every two weeks.

Results

The results of treatment with phenmetrazine and diet restriction are summarized in the Table. It will be seen that there is a comparable mean loss of weight during the month on phenmetrazine, whether it was given during the first month (6.5 lb.) or the second (6.4 lb.). However, the mean loss of weight during the month on placebo was much greater when the placebo was given first—3.3 lb.; when placebo was given after phenmetrazine there was a mean *gain* in weight during that month—0.73 lb. Consequently, the group which received placebo followed by phenmetrazine had a mean

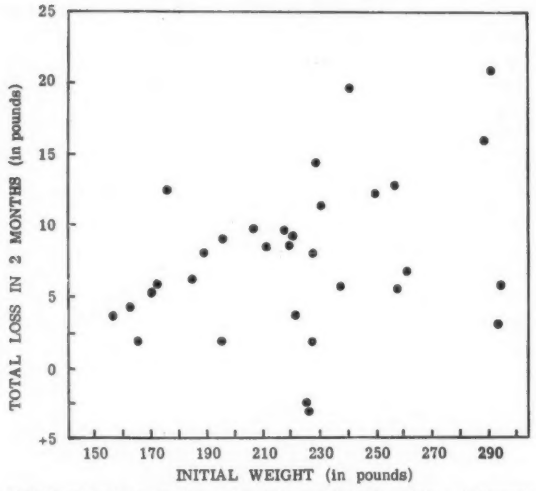
Analysis of Weight Changes (in Pounds) in Each Month on Phenmetrazine and Placebo

Order of Treatment	No. of Patients	Mean Weight Changes ±S.D. During Month on		Overall Loss ±S.D.
		Phen-metrazine	Placebo	
1st month phenmetrazine 2nd ,, placebo	16	−6·5±1·1	+0·73±0·7	2·9±0·9
1st ,, placebo 2nd ,, phenmetrazine	16	−6·4±0·8	−3·3 ±0·8	4·8±0·7
Overall mean loss±S.D. ..	32	6·4±0·7	1·3 ±0·7	

loss of weight of 4.8 lb., whereas the group which received the phenmetrazine before placebo had a mean loss of weight of 2.9 lb.

Inspection of the results suggests that those patients who were initially most overweight were those who lost most weight, and this trend is shown in the Chart, though the coefficient of correlation, $r=0.22$, is below the level of significance, $r=0.35$. To exclude this factor as a possible source of bias the loss of weight was expressed as a percentage of the initial weight:

$$\text{Percentage loss} = \frac{\text{Weight loss}}{\text{Initial weight}} \times 100.$$



Relationship between loss of weight and initial weight. Although suggestive this did not attain the level of significance.

The correlation coefficient between the percentage loss and the initial weight is not significant, and when the percentage loss was substituted for the observed loss the level of significance was of a lower order—$r=0.11$.

A statistical analysis shows that the effect of the drug compared with that of the placebo is of a high degree of significance ($P<0.001$) and that the order of treatment —that is, whether the placebo or phenmetrazine was given first—is also significant: $0.05>P>0.02$.

Side-effects.—Forty-six women received phenmetrazine in doses of 25 mg. thrice daily, and only one was unable to tolerate it; she said, "It made me feel ill." Of the 32 patients who received both types of tablets one said that phenmetrazine did not help her, whereas 15 experienced no suppression of appetite when taking the placebo. While taking the drug two patients complained of sleeplessness, two of mild "depression," and three of headache or dizziness, but these symptoms were not severe enough to make the patients abandon the treatment. Four patients complained of similar symptoms when they were taking the placebo. In no case was there any psychotic manifestation.

Discussion

It is not easy to design an ideal clinical trial that involves keeping patients on a constant calorie intake. If the trial period is too long the patients are apt to break their diet; if the period is too short the drug that is being studied may not have been given a fair chance to show its appetite-suppressing properties. For these reasons four-week periods on the drug and on the placebo were chosen. Such short periods, however, cannot demonstrate any long-term effects on phenmetrazine.

There is clearly no significant difference between the loss of weight in the two groups in the phenmetrazine month—6.5 lb. against 6.4 lb. It is evident that patients who received the placebo followed by phenmetrazine showed a more satisfactory loss of weight than those who received the phenmetrazine in the first month. The patients who received the placebo in the second month actually showed a mean gain in weight during the period of treatment, though they were unaware of the nature of the tablet. We have the impression that obese patients lose weight more satisfactorily if they have been submitted to the discipline of dieting before being given phenmetrazine.

Patients did not complain of insomnia, which sometimes occurs during treatment with drugs of the amphetamine group, in spite of the fact that phenmetrazine was given three times a day. We are of the opinion that this is a safe and effective drug, provided that the dose is not excessive.

Summary

An account is given of a controlled trial in which 32 obese patients were given phenmetrazine and placebo tablets and who completed the trial period. The patients, all of whom were at least 15% overweight, were observed for a period of two months.

25-mg. phenmetrazine tablets were given thrice daily, and in this dosage side-effects were insignificant and there was no interference with sleep.

Attention is drawn to the fact that during the second month patients on phenmetrazine lost weight whereas patients receiving the placebo in the second month gained weight. The influence of initial weight on loss of weight is considered, and there is some evidence to indicate that those who were most overweight lost more weight on treatment.

We acknowledge our indebtedness to Dr. W. R. Doll, of the Medical Research Council Statistical Unit, for his advice in the design of the trial and for his criticism in the preparation of the paper; we also thank Mrs. P. Williams for secretarial help. We are grateful to Dr. W. A. Bullen, Medical Director of Boehringer Products Division, Pfizer Ltd., for supplies of phenmetrazine and of the placebo tablets.

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PRELIMINARY OBSERVATIONS ON MANAGEMENT OF DIABETES WITH "STABINOL"

BY

M. F. HEALY, M.B., B.Ch., M.R.C.P.I.
Physician, Diabetic Clinic

AND

J. D. ARNEAUD, M.B., B.S., D.C.P.
Senior Pathologist
General Hospital, Port of Spain, Trinidad, B.W.I.

The management of diabetes by oral preparations has now become commonplace in many countries throughout the world. The literature on this subject is voluminous and the drugs in use have been given to more than half a million diabetics. Of all the hypoglycaemic agents tolbutamide has been the most widely used, and to date has the smallest incidence of abnormal side-effects. Mehnert *et al.* (1958), in a recent review of the use of tolbutamide on a group of 1,030 patients for a period of 1 to 20 months, demonstrated that it produced good control on 52.6% and fair control on an additional 18.5%.

Krall and Camerini-Davalos (1958) have reported their results with DBI in a series of 121 patients. They found it to be an effective hypoglycaemic agent in 86%, but therapy had to be discontinued in 18% because of side-effects affecting mainly the gastro-intestinal tract.

The report of Baender (1959) on the comparative toxicology and pharmacology of tolbutamide, chlorpropamide, and metahexamide, showed that compounds with greater toxicity than tolbutamide are of no particular value in the management of diabetes. He pointed out that the price to be paid for lower drug dosage should never be greater toxicity.

Davis *et al.* (1959) have reported on the use of R.P. 2259, a sulphathiadiazole (2-sulphamido-*p*-aminobenzene-5-ter-butyl-1,3,4-thiadiazole; "glipasol"). This report showed R.P. 2259 to be a relatively toxic substance with a very large incidence of liver damage.

McColl (1960) presented his findings on the hypoglycaemic activity of a group of substituted thiadiazoles, synthesized by Chubb and Nissenbaum (1959), which, like tolbutamide, have no antibacterial properties.

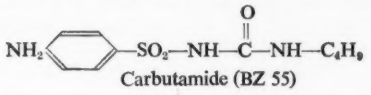
One of the most potent of these substituted thiadiazoles, was made available for this study. This was the methoxy isobutyl derivative known as FWH 114, or "stabinol." This material produces hypoglycaemia after both oral and parenteral administration in fasted rats, rabbits, and dogs. In the rabbit, for example, significant hypoglycaemia occurs within an hour and reaches a maximum in five to six hours. Normal blood-glucose levels are reached within 24 hours.

Like tolbutamide, some functional pancreatic islet tissue appears necessary for hypoglycaemic response to stabinol. It also promotes the storage of glycogen in the liver of fasted rats. With normal hypoglycaemic doses in animals stabinol appears to possess no other important pharmacological activity. Hypoglycaemia may be reversed by the administration of glucose, Stabinol is devoid of any antibacterial action.

The acute oral LD_{50} of stabinol in rats and mice is about 900 and 950 mg./kg. respectively. Chronic toxicity studies in Sprague-Dawley rats for period up to nine months at doses of 150 and 300 mg./kg./day by the oral route revealed no significant toxicity.

Only one study with oral hypoglycaemic agents has been carried out in the Federated West Indies, and that was by Tulloch (1957) with carbutamide. The dosages given were large and side-effects were common. This drug was used very little in the Federated West Indies, but widely in the Dutch West Indies (Vinke, personal communication), with remarkably few side-effects. Tulloch also reported that the type II diabetic of Hugh-Jones is the predominant type in the West Indies; in fact, more than 70% of diabetics fall in this category. This is the mild type which one might expect to respond to adequate oral hypoglycaemic medication.

Formulae of Oral Hypoglycaemic Compounds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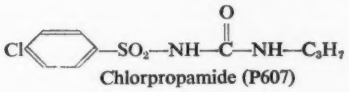
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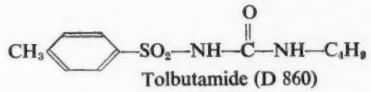
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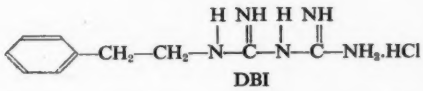
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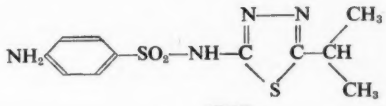
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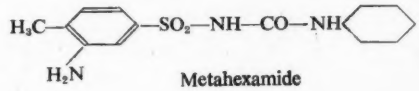
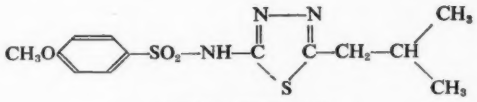

Metahexamide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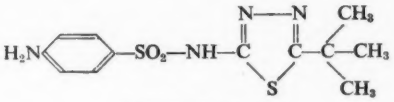
Glipasol (R.P. 2259)

Procedure

In this study 33 diabetics were maintained as out-patients from the clinic at the Port of Spain General Hospital, and were selected on the basis of the insulin dosage being used, ranging from 12 to 52 units per day. In addition the patients were selected having regard to their regular attendance, their proximity of residence to the clinic, and the absence of complications. There

were no selections as regards insulin control. Two new patients were not on insulin and were being treated by diet alone with poor control. Three patients were lost to the study.

TABLE I.—*Age Distribution*

Age	30–40	41–50	51–60	61–70	71–80
No. of patients	5	10	10	4	1

TABLE II.—*Duration of Diabetic Symptoms*

Duration (years)	<1	1	2	3	4	7	9	16
No. of patients	11	7	1	6	2	1	1	1

The ages of the patients varied from 34 to 72, with the majority (20) from 41 to 60 years of age (Table I). Duration of illness was from a few months to 16 years, most (27) falling within the category of 0–4 years (Table II). All patients, regardless of insulin dosage, were started on four tablets of 250 mg. (1 g.) of stabinol (given in a single dose in the morning) after complete blood, urine, and liver-function studies had been carried out. They were seen every other day for the first week, twice weekly during the next two weeks, once a week for the following two weeks, and then monthly until the conclusion of the trial. All patients were advised of the possibility of side-effects and were instructed to report to the clinic in the event of any untoward reactions.

General Clinical Aspects

Table III as a brief summary of pertinent clinical aspects. At the beginning of the study all patients but two were on insulin. These latter were placed on oral therapy when diet alone gave poor results. The degree of control produced by previous insulin therapy varied from fair to very good. Of the 30 patients who completed the trial, 15 (50%) showed improved control, 9 (30%) were unchanged, and 6 (20%) were not as well controlled. These results are not unlike those of McKendry *et al.* (1957) with tolbutamide therapy. By and large, the patients described themselves as feeling "much better," "more fit," and "stronger." All patients but one preferred the tablet form of therapy. This one patient appeared to be a case of primary failure.

TABLE III.—*General Clinical Aspects*

Case No.	Sex and Age	Change in Wt. in lb.	Previous Insulin Dosage	Control	Oral Dosage (g.)	Control	Result*
1	F 58	+5	I.Z.S. 28	Poor	0·250	V. good	+
2	M 36	−1½	,, 40	Good	0·125	,,	+
3	M 34	−6	,, 24	Fair	0·250	,,	+
4	M 55	+5	,, 12	Good	0·25	,,	+
5	F 43	+23	Diet	Poor	0·500	,,	+
6	M 44	+½	I.Z.S. 48	Fair	0·500	,,	+
7	M 45	0	,, 40	,,	0·250	,,	+
8	M 60	−2	,, 36	,,	0·375	,,	+
9	F 48	−3½	,, 24	V. good	0·250	,,	0
10	M 52	0	,, 20	Fair	0·125	Good	+
11	M 65	−3½	,, 24	,,	0·500	,,	+
12	F 72	+1	Diet	Poor	0·750	,,	+
13	F 46	−6	I.Z.S. 48	Fair	0·500	,,	+
14	F 55	−7	,, 40	,,	0·250	,,	+
15	F 54	+2	,, 40	,,	1·250	,,	+
16	F 55	−1	,, 24	,,	0·500	,,	+
17	F 69	+2	,, 12	Good	0·425	,,	0
18	M 40	−7	,, 18	,,	0·250	,,	0
19	F 43	0	,, 28	,,	0·750	,,	0
20	F 54	0	,, 20	,,	0·750	,,	0
21	F 42	−3	,, 48	Fair	1·500	Fair	0
22	F 43	+2	,, 40	,,	1·500	,,	0
23	F 61	−2	,, 20	Poor	1·500	Poor	0
24	F 61	0	Plain 20 / P.Z.I. 20	,,	1·750	,,	0
25	F 50	+1	P.Z.I. 24	Fair	1·750	,,	−
26	F 41	−6	I.Z.S. 40	,,	1·750	,,	−
27	F 54	+2	,, 32	,,	1·500	,,	−
28	F 38	+2½	Plain 16 / P.Z.I. 32	Good	1·750	,,	−
29	F 52	+7	I.Z.S. 40	Fair	1·750	,,	−
30	M 37	0	Plain 16 / P.Z.I. 36	Good	1·500	,,	−
31	F 42	Uncooperative	Discontinued				
32	F 46	,,					
33	F 46	Patient left Trinidad					

* Control with oral stabinol compared with previous control: + = Improved control. 0 = Unchanged. − = Not as well controlled.

Assessment of the degree of diabetic control was as follows:

Very Good.—Urine at all times "blue" (Benedict's test) or occasionally "green." Random blood-sugar not over 200 mg./100 ml.

Good.—As above, except for occasional "yellow" two or three times a month. Random blood-sugar occasionally over 200 mg./100 ml.

Fair.—Urine test mainly "blue"/"green" with "yellow" six to eight times a month. Random blood-sugar occasionally over 250 mg./100 ml.

Poor.—Urine tests occasionally "blue," usually "green"/"yellow" with "red" six to eight times a month. Random blood-sugar usually over 250 mg./100 ml.

Biochemical Aspects

Five liver-function studies were performed before starting oral therapy, as well as at the conclusion. These were "bromsulphalein" retention, bilirubin, thymol turbidity, zinc sulphate turbidity, and colloid gold flocculation. The results of these tests, both before and after, were essentially negative. Blood of each patient was analysed before and after for the following constituents: urea, total protein, albumin, globulin, and haemoglobin. These were essentially normal. The cellular elements in the blood were examined before and after the trial and no abnormalities were detected. The urine of each patient was examined before, during, and after the trial, and no abnormalities attributable to the drug were found. The urine was examined regularly by means of "clinistix," and the use of this method of glucose determination proved very satisfactory. Throughout the trial selected specimens of urine were also checked with Benedict's reagent and there was satisfactory correlation between both tests.

Discussion

Since the advent of the use of sulphonylurea compounds in the management of diabetes, most diabetics have been grouped either as the juvenile or the maturity onset type. This is obviously unsatisfactory as a scientific method of classification, since it gives no indication of the severity of the individual's disease. However, most workers have found that the diabetic whose disease became apparent late in life was most likely to respond to oral therapy. This was considered when patients were chosen for this study. As we expected, the majority did respond and were as well controlled as on insulin, and in some cases control was better. Many workers have shown that there is no direct correlation between insulin dosage and that of various forms of oral therapy. This holds true in this study, as is shown in Table III.

There are, of course, obvious advantages to the management of diabetes with oral preparations in countries such as the British West Indies, where the use of sterile parenteral equipment becomes a major problem. Most of the patients are afraid or unable to give themselves insulin, and most relatives or neighbours are not prepared to learn. Because of these factors at this clinic,

most of the patients on insulin attend daily for their injection. The cost of transport, tropical rain, and any mild intercurrent illness resulted in irregular attendance. In the long run, therefore, management with oral preparations would probably be cheaper for the patients.

While not all diabetics will respond to oral therapy, this study shows that a large number of selected patients will respond satisfactorily to this particular drug. In view of its safety, as evidenced by liver-function, blood, and urine studies, stabinol appears to be a worth-while addition to the therapy of diabetes.

Summary

The antidiabetic effect of stabinol has been evaluated on a group of 33 patients with diabetes of the maturity onset type. Of this group three were lost to the study.

Of the remaining 30 patients, 15 (50%) were better controlled with the oral agent than they had previously been on insulin therapy, 9 (30%) were controlled equally well on either regimen, and 6 (20%) were not as well controlled on oral therapy as they were on insulin therapy.

Liver-function studies and blood and urine findings remained normal throughout the study.

There were no side-effects or abnormal reactions.

We wish to thank Frank W. Horner Ltd. for supplies of stabinol used in this study, and for a grant to one of us (M. F. H.); Ames Company for supplies of clinistix; Dr. J. Ray MacDougal, medical director, Frank W. Horner Ltd., for advice and help; and the patients who volunteered for the trial. We are grateful to the Minister of Health, Water and Sanitation, and the Director of Medical Services for permission to publish these findings.

ADDENDUM.—Since the completion of this trial in April, 1959, 16 of these patients have been maintained on stabinol with very good or good control for a further eight months. They have been on the drug for over one year.

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Medical Memoranda

Callosities with Horny Plugs

Patients are often sent to dermatological departments with the diagnosis of plantar wart, when the lesion consists of a callosity in the centre of which is a little horny plug (Fig. 1). The callosity usually lies under the heads of the second and third metatarsals and may be associated with some degree of hammer-toe in the second digit. The condition is described in some orthopaedic books, where it is thought to be a form of callosity, but often it is diagnosed by general practitioners as a plantar wart; some dermatologists believe this is correct. The treatment of these two conditions is so different—a wart being removed whilst a callosity requires an orthopaedic adjustment—that I have investigated a number of these lesions to see if it is possible to decide their true nature.

The histology of a plantar wart is characteristic, with ballooning of the cells and fragmentation of the nuclei spreading right up into the horny layer and giving a very bizarre appearance. In contrast to this the horny plug (Fig. 2) under discussion shows perfectly regular parakeratosis with uniform non-fragmented nuclei and a well-formed horny layer without any ballooning of cells or vacuolization. The column of parakeratosis

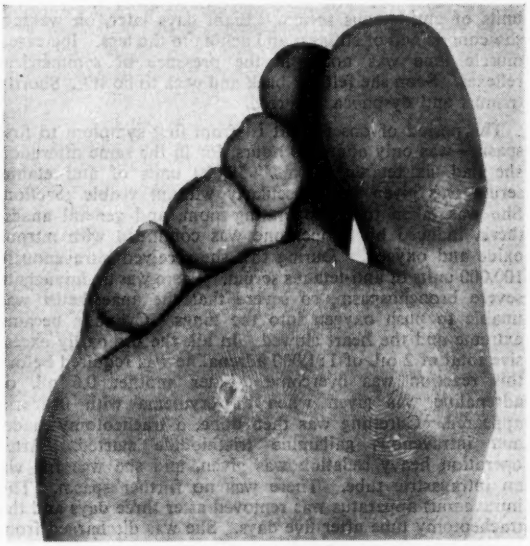

FIG. 1.—Callosity with little horny plug in centre.

FIG. 2.—Photomicrograph of section of horny plug.

ends more or less abruptly and passes into the hyperkeratotic horny layer of the surrounding callosity.

It seems clear, therefore, that these lesions are not plantar warts and that such treatments as radiotherapy or even curettage are unlikely to produce a permanent cure. They should be dealt with along the usual orthopaedic lines for a callosity.

F. F. HELLIER, O.B.E., M.D., F.R.C.P.,
Dermatologist, the General Infirmary at Leeds.

Tetanus Eight Days After Administration of Anti-tetanus Serum

The following case, in which tetanus occurred after the prophylactic subcutaneous injection of 1,500 units of anti-tetanus serum, may be found of interest.

CASE REPORT

After an injury in 1952 a young married woman received an injection of anti-tetanus serum, but did not subsequently receive active immunization with toxoid. Nearly three years later she was admitted to the care of an honorary gynaecologist at the Launceston General Hospital with a diagnosis of incomplete septic abortion. She was given 1,500 U.S.A. units of anti-tetanus serum. Eight days later, on waking, she complained of stiffness and aching in the legs. Increased muscle tone was noted in the presence of symmetrical reflexes. Soon she felt her back and neck to be stiff. Shortly trismus and dyspnoea occurred.

The period of onset—that is, from first symptom to first spasm—was only about 10 hours, for in the same afternoon she had six tetanic spasms. 50,000 units of anti-tetanus serum was given intramuscularly without visible reaction. She was taken to the operating-room, and general anaesthesia induced by thiopentone was continued with nitrous oxide and oxygen. During this she received intravenously 100,000 units of anti-tetanus serum. There was an immediate severe bronchospasm, so severe that the anaesthetist was unable to push oxygen into the lungs. Cyanosis became extreme and the heart slowed. In all, the ordinarily excessive total of 2 ml. of 1:1,000 adrenaline was required before this reaction was overcome. Later another 0.6 ml. of adrenaline was given when an erythema with urticaria appeared. Curetting was then done, a tracheotomy made, and intravenous gallamine triethiodide started. After operation heavy sedation was given, and she was fed via an intragastric tube. There was no further spasm. The intravenous apparatus was removed after three days and the tracheotomy tube after five days. She was discharged from hospital 19 days after the spasms.

COMMENT

Probable Effects of Previous Horse Serum.—Bigler and Werner (1941) showed that effective protection after a dose of 1,500 units of anti-tetanus serum may last up to three weeks. This refers, however, to the patient who has not already been sensitized to horse serum, and Ackland (1959) has recalled that Sacquepée and Jude as early as 1937 warned that antitoxin given to an animal or person who has had previous serum may result in rapid loss of the antitoxin. This patient had received previous anti-tetanus serum, and developed tetanus only eight days after her second injection of anti-tetanus serum.

Similarities to a Previous Report.—A report similar in two respects to that above was made by Littlewood, Mant, and Wright (1954). They reported the case of a schoolboy who injured his hand while experimenting with a home-made bomb. He received 1,500 units of anti-tetanus serum, penicillin, and appropriate surgical treatment, including skin grafting. About six months later he was readmitted with similar injuries caused by the explosion of another home-made bomb. He again received 1,500 units of anti-tetanus serum, penicillin, and surgical treatment, including another graft. On the twelfth day he developed trismus and stiffness of the erector spinae muscles. Desensitization was attempted, and, when thought complete, 0.1 ml. of horse serum was given intravenously. This produced a severe generalized reaction. Eventually 100,000 units of horse serum was given intravenously, but the signs of tetanus increased in severity and the boy died 17 days after his injury.

Wright (1958) proposes that the reason for the failure of the second injection of anti-tetanus serum was that this serum, six months before, had induced a sensitization with consequent accelerated destruction of the specific horse globulin. The woman now reported had also had previous anti-tetanus serum, and, like the boy, had a generalized reaction after receiving anti-tetanus serum intravenously, the route of administration long known to be the most dangerous in this respect (Bruce, 1920). A second very disturbing feature common to both is the development of tetanus within 12 days of a second dose of anti-tetanus serum, and it may be that Wright's explanation applies to the woman now reported. However, experiments recently carried out in Melbourne on the level of anti-tetanus serum in man after injection of 1,500 units did not show any significant difference in antitoxin levels between normal and sensitized individuals (S. D. Rubbo and J. C. Suri, 1960, unpublished work).

Active Immunization after Recovery from Tetanus.—Several writers heed the experience of Martin and McDowell (1954), who reported a second attack of tetanus in the same person. Another example of recurrent tetanus was reported by Beare (1953). Cooke and Jones (1943) state that a demonstrable antitoxin does not persist in the blood after recovery. In four children with clinical tetanus they found that antitoxins failed to appear: the amount of toxin absorbed during a tetanus infection was so small as to produce no primary antigenic stimulus. Hence it appears that an attack of tetanus does not confer immunity. Accordingly the patient above reported was advised to obtain active immunization with tetanus toxoid.

Double Active Immunization to Follow Horse Serum.—Littlewood *et al.* (1954) urged that anyone who has received horse serum should be actively immunized not only against tetanus but also against diphtheria. Diphtheria antitoxin, like tetanus antitoxin, is produced in horses, and a second injection of this animal's protein may result in its very rapid elimination from the body, thus running the risk of greatly shortening the duration of passive immunity (Wright, 1958). It appears desirable, even if only to prevent reactions to horse serum, that those who have received horse serum should have the Schick test, and the susceptible should then have the Moloney test and be considered for active immunization with diphtheria toxoid.

W. W. WOODWARD, M.B., F.R.C.S., F.R.A.C.S.,
Honorary Surgeon to In-patients,
General Hospital, Launceston, Tasmania.

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The Communicable Disease Center, Georgia, U.S.A., has issued a complete list of films available from its film library as on June 1, 1960. Details are available from the Center, Atlanta 22, Georgia, U.S.A. (attention Audiovisual).

Reviews

FEET

The Foot and Ankle. Their Injuries, Diseases, Deformities, and Disabilities. By Philip Lewin, M.D., F.A.C.S., F.I.C.S. Special drawings by Harold Laufman, M.D., F.A.C.S. Fourth edition. (Pp. 612; illustrated. £5 5s.) London: Henry Kimpton. 1959.

Surgery of the Foot. By Henri L. DuVries, M.D. Foreword by Karl A. Meyer, M.D. Introduction by Edward L. Compere, M.D. (Pp. 494; illustrated. 93s. 6d.) London: Henry Kimpton. 1959.

It has often been said that although the foot is such an important structure to man (the only mammal with permanent bipedal progression) there have nevertheless been published very few books devoted exclusively to its functions and disabilities. Perhaps this accusation is not entirely true, for there have certainly been several volumes published in the United States on this subject and a lesser number in this country. The unusual thing about the two books now under review is not that they both appeared in the same year but that they both came from Chicago. One must not deduce from this, of course, that the citizens of that town are more prone to, or more conscious of, foot troubles than the rest of the populace.

Dr. Lewin's book *The Foot and Ankle* has now reached its fourth edition; we had the opportunity of giving a very favourable review of the first edition in 1940. In the main this work, which is now well known in this country as well as in the States, retains its general character, but there has of necessity been some change in emphasis to correspond to the advances in diagnosis and treatment which have occurred over the years. It must be recognized that this book covers a wider scope than that of most other works on the foot, as indeed the title implies. For instance, fractures and other conditions of the lower tibia and the ankle-joint are dealt with, as is also the earlier management of acute poliomyelitis as well as the surgery of the later residual deformities. A slight criticism may be offered of the juxtaposition of the description of Morton's metatarsalgia with an immediately following section entitled "The Morton Syndrome," which describes the condition of short hypermobile first metatarsal upon which the late Dr. Dudley Morton laid such stress, without any indication that there were two Mortons separated by an interval of nearly half a century. But this is a very small historical point. A characteristic of Lewin's book has always been the aphorisms—"Pedigrams or Footnotes" he calls them—in the final pages, such as "Take the arch out of your back and put it in your foot," "There is no shoe too small for an ambitious female's foot"; also characteristic are the framed insets in the text giving in a few words a summary of important points in the sections.

We retain our original opinion that this book can be recommended with confidence as an excellent guide to diseases of the foot and ankle.

In contrast *Surgery of the Foot* by Henri DuVries limits itself to the foot proper. This is a new book, and in an introduction Dr. Compere tells us that the author had his early training in chiropody and subsequently qualified in medicine. It is therefore all the more surprising to find that there is practically no reference to chiropodial treatment—as we understand it in Britain—for any condition, and that the emphasis throughout is on operative treatment. Perhaps this is to be explained by the difference in the scope of chiropodial (often called podiatric in the States) practice in America from the more limited scope in this country. There open operations for many foot deformities are allowed, whereas here such operations are prohibited to the chiropodist. The title of the book has been literally interpreted by the author, but we cannot help feeling that some account of the methods of chiropodial treatment by means of padding and so on would have placed the purely surgical methods in a better perspective.

Probably few surgeons in this country would consider a "plantar condylectomy" for the treatment of even advanced plantar callosities, since it would seem that the causative stresses occur at the "take off" when the metatarsals are almost vertical and the pressure and friction occur on the heads of the metatarsals rather than the condyles. However, the author claims complete success for this operation in 70% of cases. This example, one of many, is given to illustrate the difference in practice between the two countries. Then there are discrepancies in the text—which is not always easy to follow—thus, "malignant melanoma of the foot should be widely excised and regional lymphatics dissected" (p. 133), but for malignant subungual melanoma (in the reviewer's experience a very malignant form) "the treatment is by local excision" (p. 207). Is it a strictly limited interpretation of the title which has led the author to omit any reference to intermittent claudication in the foot, or to hyperhidrosis (except for one word under frostbite) and many other troublesome foot conditions and yet to include many which are rarely seen, at any rate in this country?

The book is extremely well illustrated and beautifully produced; it is quite evidently the outcome of a very wide experience with an abundance of material.

NORMAN C. LAKE.

TOOLS FOR THE BIOLOGICAL JOB

Tools of Biological Research. Edited by Hedley J. B. Atkins, D.M., M.Ch.Oxf., F.R.C.S.Eng., Hon.F.A.C.S. Introduction by Sir Cyril Hinshelwood, P.R.S. (Pp. 183+xvi; illustrated. 37s. 6d.) Oxford: Blackwell Scientific Publications. 1959.

This book contains ten papers on methods read at a symposium at Guy's Hospital in October, 1958. The symposium was designed to give members of the Surgical Research Society information about some of the new techniques now being used in medical research. The papers are preceded by an admirable introduction by Sir Cyril Hinshelwood, who speaks of the interplay of strategy and tactics in medical research, and of the need for the research worker not only to be an expert in one field but to have, in addition, a superficial acquaintance with the outlines of many. The transfer of a technique from the field in which it was developed to an entirely different one may lead to rapid advances in knowledge.

The successive chapters deal with the design of experiments, flame photometry, electromanometry, tissue culture and transplantation, electron microscopy, phase contrast and interference microscopy, electrophoresis, image intensification in radiology, and mass spectrometry. They are concisely and clearly written, with sufficient references to provide access to the literature. The success of the symposium is indicated by the fact that a second publication on the same lines is projected.

Heads of research departments are in much the same position as those of supply departments in the last war: their young men can always spend more money than they can find. The difficulty is to know what is instrumenta-

tion for instrumentation's sake, and what is truly an aid to production. This book gives a useful perspective on the technical demands of modern research and will persuade the seniors to make even more strenuous efforts to provide their juniors with the tools for the job.

L. J. WITTS.

FLUORIDATION

Fluoridation. Errors and Omissions in Experimental Trials. By Philip R. N. Sutton, D.D.Sc.(Melb.), L.D.S.(Vic.). (Pp. 83+vii. 8s. 6d.) London: Cambridge University Press. 1959.

This is a monograph criticizing the results of the American investigations into the efficacy of fluoridation of water supplies for the prevention of dental caries. Such a monograph can only be convincing when it is itself free from significant errors and omissions. The bibliography extends over three pages, but this is modest in view of the immense number of publications on the subject. In a critical monograph, such as this, one might hope to find that the author had corresponded with key investigators to clarify points of importance. It is very disappointing to find no record of such efforts being made. This could well account for the failure to quote several key publications which make some of his criticisms unnecessary. There can be little doubt that some of the criticisms are valid, but to conclude from this that there is no basis for assessment of the value of fluoridation of water supplies is hardly justifiable. Recognition of the value of fluorides in reducing the incidence of dental caries is based primarily on observations of communities where fluoride is present naturally in the water supply. These studies have been supported by various laboratory assessments of the effect of fluoride on mineral solubility and on enzyme processes. In such experiments more control is possible than in clinical surveys which involve groups of investigators recording the dental state of children from populations which become increasingly mobile over the years of study.

The rigid controls which would have satisfied the author are almost impossible to obtain in the protracted studies required for the investigation of this type of problem, but this shortcoming should not be allowed to vitiate the general and concordant findings of the five investigations criticized. The general order of reduction of caries incidence by 40% or 50% has been confirmed elsewhere in the U.S.A., and more recently in other parts of the world in reports which are not mentioned.

Most of the criticisms have been directed at the analyses of results from the control communities and quite large variations in caries rates and in water analyses do seem to have been accepted as comparable by the investigators concerned. Nevertheless, the variations quoted could hardly invalidate the results in view of the large reduction in the incidence of caries found in all five studies.

If the author has had no opportunity of conducting such an investigation to show how it should be done, he would have been wiser to confine his criticisms to points of real substance and to take a more generous view of the sincerity and ability of those whose work he criticizes. He would have made his views more convincing if he had avoided the emotional connotations of many of his subheadings, e.g., "fluctuations disguised."

It is a great pity that this book has dealt with so much adverse detail while ignoring the large amount of evidence for the success of caries prevention by fluoridation of the water supplies.

A. I. DARLING.

BIOCHEMICAL PHARMACOLOGY

An Introduction to Pharmacology. By J. J. Lewis. Foreword by Stanley Alstead, C.B.E., M.D., F.R.C.P.Ed., F.R.C.P.Lond., P.R.F.P.S. (Pp. 826+xii; illustrated. 55s.) Edinburgh and London: E. and S. Livingstone, Ltd. 1960.

Pharmacology is moving increasingly towards biochemical methods and concepts. This development is welcome and indeed necessary, since its ultimate aim is the definition of drug action on the target cell. This book stresses the chemical and biochemical approach. Structural formulae of most of the compounds mentioned are given, though it seems unnecessary to show them twice as is done in the case of oxytocin and streptomycin. The relationship of drug actions to ion mechanisms is well explained. The degradative metabolism of drugs are clearly described but the emphasis is again on chemical changes. When discussing the fate of barbiturates, for example, the role of the liver, of the body fat depots, and of the blood-brain barrier is not mentioned. Structure-action relationships are fully considered. Less welcome are the long lists of related drugs: for instance, the list of "some of the commoner atropine-like compounds and allied drugs" contains 36 substances; this is not needed in an "introduction." Moreover, there are sometimes errors in these tables: "Gardenal" (p. 243), for example, is phenobarbitone, not methylphenobarbitone. Comments on the pharmacological properties of drugs are, as a rule, rather brief, but there are some good diagrams showing the different sites of action of therapeutically related substances—e.g., the tranquillizers and the analeptics. Reference to bio-assay methods are adequate, and a short section on the statistical evaluation of results is included.

This is an interesting book. Its strong chemical bias may make it suitable for non-medical undergraduates—for students of pharmacy, for instance, and biochemists interested in pharmacology. Such readers would, however, miss reference to original papers or, at least, to recent review articles. The medical student is unlikely to know enough organic chemistry to appreciate the information offered. He may also be dismayed by the very great number of drugs mentioned, though this feature may make the book a useful source of reference for his teachers.

H. HELLER.

DENTAL ATLAS

An Atlas of Dental and Oral Radiology. By Sydney Blackman, M.R.C.S., L.R.C.P., D.M.R.E.(Camb.). (Pp. 384+xi. 84s.) Bristol: John Wright and Sons, Ltd. 1959.

This atlas consists, very largely, of photographic reproductions from radiographs with explanatory texts. On the whole the quality of the reproductions is excellent, and both the author and the publishers are to be congratulated on the clarity of illustration.

The book is divided into three parts, the first being concerned with the eruption and development of teeth; the second with inflammatory and traumatic lesions of teeth and jaws; and the third with cysts and new growths involving teeth, jaws, and soft tissues. In the first section the normal radiographic appearances of the teeth and jaws are discussed and illustrated. In each section there is a short foreword describing the conditions to be illustrated with an explanation of the connexion between the pathology and the radiographic appearances. There is a remarkably complete collection of both common and rare conditions, and it should prove a useful book for reference.

It is a pity that the text is not always of the same quality as the photographs. Apart from minor criticisms, there are some remarkable and very misleading statements: on page 335, for instance, it is said that the true growths of fibroid epulis, benign and malignant, arise from any of the constituent tissue formations found in the mouth, and are classified as epulides. The suggestion that a fibroid epulis can be malignant is entirely incorrect. Figure 706 is described as multiple osteomata, but, as the bone of the mandible appears largely destroyed with what looks like an osteomyelitic process with an unerupted tooth, it is scarcely typical of multiple osteomata; while Fig. 696 looks far more like an odontome than an osteoma.

Many other examples of apparent carelessness, either in the text or in the choice of photographs to illustrate certain conditions, could be quoted. It is to be hoped that in future editions more critical attention will be given to preparation, as the book is basically good and useful.

ALEXANDER B. MACGREGOR.

THE STUDENT'S MENTAL HEALTH

The Student and Mental Health. An International View. Proceedings of the First International Conference on Student Mental Health, Princeton, N.J., September 5–15, 1956. Edited by Daniel H. Funkenstein, M.D., assisted by Stella B. Hanau, A.B., and George H. Wilkie, M.D. (Pp. 495+xxv. 35s.) London: H. K. Lewis and Co., Ltd., for the World Federation for Mental Health. 1959.

This is the report of the International Conference on the Mental Health of the Student, held at Princeton in 1956. There is an inevitable difficulty in making a readable book out of proceedings of a major conference: there are so many views and cross-currents of thought; there is so much compressing to be done. Dr. D. H. Funkenstein, the editor, has made a most praiseworthy job of his difficult assignment and has produced a book that will be read, enjoyed, and kept by all directly interested in student health problems. The general medical or psychiatric reader will necessarily get less from the work.

Erikson's exposition of the "adolescent identity crisis," from which most of the conference's theoretical orientations came, has been published elsewhere, so have Fromm's stimulating views on the relationship of society to neurotic sickness. Dr. Henry Murphy's beautiful account of the cultural factors in the mental health of Malayan students is a study in social psychiatry that may well prove the most rewarding chapter for the ordinary reader.

NICOLAS MALLESON.

A Short History of Nursing by W. R. Bett is not so much a short history of nursing as an entertaining scrapbook on the subject. One forgives its occasional perfunctoriness for the romantic description of how William Stewart Halsted, the eccentric and difficult surgeon, invented rubber gloves to protect the hands of Caroline Hampton, his theatre nurse, whom he later married, or for Gamgee's account of gamgee tissue: "There must be no squeezing like that of an old college friend's hand, when seen after a long absence. The soothing surgical pressure is like that which you interchange with the hand of a lady, when the pleasure of meeting her is tempered by a respectful regard. Your hand adapts itself to hers, and gently presses it wherever it can touch it, but nowhere squeezes it for fear of offending. Such pressure when employed by the surgeon in the treatment of injuries always soothes and heals." (Faber and Faber; 125 pp.; index; price 12s. 6d.)

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

A Handbook of Paediatrics for Nurses in General Training. By Q. M. Jackson, D.N.(Lond.). Second edition. (Pp. 105+viii. 12s. 6d.) London: H. K. Lewis and Co., Ltd. 1960.

The Freudian Ethic. By Richard La Piere. (Pp. 299+x. 25s.) London: George Allen and Unwin, Ltd. 1960.

Proceedings of a Symposium on the Central Nervous System Control of Circulation, held in Washington, D.C., November 1-3, 1959. Edited by Ludwig W. Eichna, M.D., and Lieutenant Donald G. McQuarrie, M.C., U.S.N.R. ***Physiological Reviews, April 1960, Supplement No. 4.*** (Pp. 311+viii; illustrated.) Washington, D.C.: American Physiological Society. 1960.

Leitfaden der Gewebezüchtung. By Dr. Jaroslav Řeřábek and Dr. Emmy Řeřábek. (Pp. 370+xiv; illustrated. DM. 64.90.) Jena: VEB Gustav Fischer Verlag. 1960.

Collected Papers of the Mayo Clinic and the Mayo Foundation. Volume 51, 1959. (Pp. 825+xv; illustrated.) Philadelphia and London: W. B. Saunders Company. 1960.

Margaret McMillan: "The Children's Champion." By G. A. N. Lowndes, M.C., B.Litt., J.P. (Pp. 110; illustrated. 15s.) London: Museum Press, Ltd. 1960.

The Sturge-Weber Syndrome. By G. L. Alexander, M.D. (Edin.), F.R.C.S.Ed., F.R.C.S., and R. M. Norman, M.D. (Bristol), M.R.C.P. (Pp. 95+vii; illustrated 32s. 6d.) Bristol: John Wright and Sons, Ltd. 1960.

Toxicologia. By Alfredo Buzzo and Miguel Fernando Soria. Fifth edition. (Pp. 658+xv; illustrated.) Buenos Aires: Lopez Libreros Editores S.R.L. 1960.

The Neurological Examination of the Infant. By André-Thomas and Mme. Saint-Anne-Dargassies. Edited by R. C. MacKeith, P. E. Polani, and E. Clayton-Jones. (Pp. 50; illustrated. 5s.) London: National Spastics Society. 1960.

Office Diagnosis. By Paul Williamson, M.D. Illustrated by Ann Williamson. (Pp. 470+xiv. 87s. 6d.) Philadelphia and London: W. B. Saunders Company. 1960.

Current Surgical Management II. A Book of Alternative Viewpoints on Controversial Surgical Problems. Edited by John H. Mulholland, M.D., Edwin H. Ellison, M.D., and Stanley R. Friesen, M.D. With 50 contributors. (Pp. 348+xxi; illustrated. 56s.) Philadelphia and London: W. B. Saunders Company. 1960.

Herz- und Kreislaufstörungen im Sauglings- und Kindesalter By Professor Dr. P. Gegesi Kiss and Dr. Gy Szutrély. Chapter on *Surgical Treatment* by Professor Dr. J. Kudász. (Pp. 879; illustrated.) Budapest: Publishing House of the Hungarian Academy of Sciences. 1960.

The New Public Health. An Introduction for Midwives, Health Visitors and Social Workers. By Fred Grundy, M.D., M.R.C.P., D.P.H. Fifth edition. (Pp. 206+xii; illustrated. 21s.) London: H. K. Lewis and Co., Ltd. 1960.

The Use of LSD in Psychotherapy. Transactions of a Conference on d-Lysergic Acid Diethylamide (LSD-25), April 22-24, 1959, Princeton. Edited by Harold A. Abramson, M.D. (Pp. 304; illustrated. $5.) New York: Josiah Macy, Jr., Foundation. 1960.

Clinical Obstetrics and Gynecology. Volume 3, No. 2. ***Physiology of Pregnancy.*** Edited by Ernest W. Page, M.D. ***Endometriosis.*** Edited by Charles S. Stevenson, M.D. (Pp. 269–536; illustrated.) New York: Paul B. Hoeber, Inc. 1960.

Radiation: Use and Control in Industrial Application. By Charles Wesley Shilling, M.D., Sc.D. (Pp. 223+viii; illustrated. $6.75.) New York and London: Grune and Stratton. 1960.

Advances in Pediatrics. Edited by S. Z. Levine, with five associate editors. Volume XI. (Pp. 285; illustrated. 68s.) Chicago: Year Book Publishers, Inc. London: Interscience Publishers, Ltd. 1960.

And I Shall Be Healed. A Story of a Miracle Cure. By Edeltraud Fulda. Translated by John Coombs. (Pp. 290. 21s.) London, Melbourne, Toronto: Heinemann. 1960.

The Year Book of Endocrinology. (1959–1960 ***Year Book*** Series). Edited by Gilbert S. Gordan, M.D., Ph.D., F.A.C.P. (Pp. 384; illustrated. 60s.) Chicago: Year Book Publishers, Inc. London: Interscience Publishers, Ltd. 1960.

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POOR SERVICE IN CASUALTY

Yet another report[1] amply confirms the grave disquiet[2] expressed in recent years about the organization for the treatment of casualties in Britain. Entitled *Casualty Services and their Setting —A Study in Medical Care*, this valuable study by the Nuffield Provincial Hospitals Trust has appeared barely two years after the investigation began. The report is the work of a team consisting of two senior general surgeons, an orthopaedic and a plastic surgeon, a general practitioner, and an expert in social medicine. They visited fourteen representative areas in England with a total population of 5 million, and the casualty departments examined were in twenty main hospitals and several smaller ones. Transport to hospital in these areas could vary from a weekly bus to a highly organized city service.

The survey shows that with some important exceptions the casualty services are badly housed in poor accommodation and with poor equipment, and often staffed by inadequately trained junior doctors receiving little help from consultants. The term "casualty" is itself vague and unsatisfactory, for a patient with this label may be injured, or may be suffering from a medical emergency or a trivial ailment. About 11 million "casualty" attendances are made yearly (one-third of the total in- and out-patient attendances). Despite the fact that a substantial number of these are the injured from road accidents, the casualty services have not made much progress this century, and there has been little agitation for improvement until the recent Memorandum on Accident Services of the British Orthopaedic Association.[3]

The team devised a useful visual rating chart based on a comprehensive range of requirements for good casualty care, including consultant cover, junior staff, accommodation, equipment, records, and so on. In the majority of departments many of these items received a low rating, but an important exception was the quality of the casualty sister, who was usually excellent and often the keystone of the department. Interest in control of infection and rehabilitation and follow-up by the medical staff were usually poor. Consultants rarely appeared for a regular session in many casualty departments.

The difficulties of obtaining junior hospital staff are notorious, and the report warns that overseas graduates may not always be available in their present numbers. Another common problem is the difficulty of covering night time and week-ends in casualty departments. In a number of hospitals the lack of experienced casualty officers has been overcome by the appointment of a senior hospital medical officer, but the disadvantage of this is that the job is often regarded as a dead-end one. Training of junior staff was usually found to be inadequate, and the report suggests that the Royal College of Surgeons might review its designated casualty posts in the light of training facilities. A teaching hospital included in the survey experienced none of these problems, but the team found very little liaison between that hospital and its neighbours so far as the casualty services were concerned.

In their studies of the case load on casualty departments the surveyors found that in some areas good co-operation with the general practitioners could reduce the load, and in other areas industrial health services had the same effect. Casualty departments varied from opening their doors to all patients to insisting on admission by doctor's letter only. On average, 20% of patients came with a doctor's letter. The report finds that liaison between general practitioners and hospitals is sometimes poor, and diagnostic facilities (pathology and *x*-rays) are often not made available at the hospital for general practitioners. In some areas the general practitioner works on a sessional basis as casualty officer, and this often seems a very happy arrangement.

The report suggests that regional hospital boards should make similar surveys of their areas with a view to urgent executive action. The lack of organized research is likely to hamper the development of the accident services. It is impracticable to lay down a definite pattern for the future, since conditions vary so widely, but it is inevitable that the treatment of casualties should be concentrated in certain hospitals and that some casualty departments will have to close. The report suggests a catchment area of 300,000 people for the main accident unit in a general hospital.

The reorganization of the casualty services in the National Health Service should not present insuperable difficulties, and this report from the Nuffield Provincial Hospitals Trust should finally convince the many lay and few medical members of hospital committees who so far are opposed to the policy of

[1] *Casualty Services and their Setting—A Study in Medical Care*, 1960. Published for the Nuffield Provincial Hospitals Trust by Oxford University Press, London. Price 7s. 6d. net.
[2] See leading article, *Brit. med. J.*, 1959, **2**, 1009.
[3] British Orthopaedic Association, *Memorandum on Accident Services*, 1959.

treating the injured in major units, with resultant closure of smaller units. A thorough overhaul of existing arrangements is certainly required if an efficient 24-hour casualty service is to be provided. Among other defects, the present distribution of orthopaedic and plastic surgeons is patchy and not related to population and demand, and if the improvements suggested in the report are to be made there will have to be many more appointments in these specialties. It is to be hoped also that more industrial health services will be able to provide a prompt and efficient casualty service and thus to reduce the load on hospitals.

TESTING LUNG FUNCTION

Physicians and surgeons caring for patients with respiratory disease have generally been slow to realize the importance of defining the functional disorder in their patients in addition to the structural abnormality and its aetiology. It was formerly thought sufficient to reach a morphological diagnosis, the keystone of which was the radiological appearance, and to judge the patient's progress by similar criteria. This attitude is only slowly changing.

In contrast, it has long been standard practice to think of disorders of the heart from the functional aspect as well as the structural, so that one speaks, for instance, of "left ventricular failure due to aortic stenosis." Similarly, arteriosclerosis of the femoral artery would not be regarded as a complete diagnosis without a definition of the extent of impairment of blood supply to the limb. Few would care to manage a patient with renal disease without some knowledge of the functional state of the kidneys based on examination of the urine and biochemical measurements on the blood. Yet the same physicians may treat a patient with ventilatory failure due to chronic bronchitis and a superimposed infection while remaining ignorant of the extent to which the levels of the blood gases are disturbed.

Last autumn speakers at a symposium at Birmingham discussed the assessment of respiratory function, and their papers have recently been published.[1-5] The objective of the assessment is to define all phases of the function of the lungs. The papers note those phases which are at present susceptible to testing and describe the scope of the techniques available. They emphasize how much valuable information can be derived from the use of a few relatively simple tests. The function of the lungs may be conveniently divided into ventilation, diffusion, and perfusion, any one or more than one of which may be disordered in a particular patient.

Ventilation is concerned with the transport of gas between the atmosphere and the alveoli, so that levels of oxygen and carbon dioxide are maintained in the alveoli which will permit optimal gas exchange with the blood in the pulmonary capillaries. The best indication of the adequacy of ventilation is the level of the alveolar, or the arterial, carbon-dioxide tension. This is dependent only on the rate of elimination of carbon dioxide and the alveolar ventilation. A significant rise in the tension of the alveolar carbon dioxide therefore indicates that the ventilation is insufficient for the metabolic requirements of the patient. To measure the tension of arterial carbon dioxide is not difficult, but it is time-consuming. For this reason the simple and rapid rebreathing method described by E. J. M. Campbell and J. B. L. Howell[6] is a valuable advance and brings the measurement within the scope of any ward side-room. There are many causes of underventilation, but the commonest is obstruction of the airways due to chronic bronchitis and emphysema or to asthma. The degree of obstruction may be estimated readily from a fast expiratory spirogram[7,8] or more simply, but probably with less discrimination, by the Wright peak-flow meter.[9]

Diffusion is concerned with the transfer of gas between the alveoli and the blood in the pulmonary capillaries. This may be impaired either by a reduction in the area available for diffusion, as for instance when a part of the pulmonary vascular bed is obstructed by an embolus, or by a thickening of the alveolar-capillary membrane. This may result from pulmonary oedema or from the presence of abnormal tissue in the alveolar septa as seen in sarcoidosis, berylliosis, certain forms of carcinomatosis, and a number of other diseases. The diffusing capacity of the lungs can be measured with comparative ease, but impairment of diffusing capacity may be strongly suspected if the arterial oxygen saturation falls considerably during exercise when there is no evidence of a veno-arterial shunt.

Perfusion is concerned with the even distribution of the pulmonary blood flow to the alveoli in proportion to their ventilation, and at normal levels of pressure within the pulmonary circulation. The evenness or otherwise of blood flow is not at present easily determined, but many of the conditions in which it is uneven are associated with pulmonary hypertension. Though the presence of this may be suspected from clinical examination or electrocardiography, it can

[1] Arnott, W. M., *Brit. J. Dis. Chest*, 1960, **54**, 106.
[2] Bishop, J. M., ibid., 1960, **54**, 113.
[3] Butler, J., ibid., 1960, **54**, 118.
[4] Harris, P., ibid., 1960, **54**, 129.
[5] Bishop, J. M., ibid., 1960, **54**, 133.
[6] Campbell, E. J. M., and Howell, J. B. L., *Brit. med. J.*, 1960, **1**, 458.
[7] Gaensler, E. A., *Amer. Rev. Tuberc.*, 1951, **64**, 256.
[8] Leuallen, E. C., and Fowler, W. S., ibid., 1955, **72**, 783.
[9] Wright, B. M., and McKerrow, C. B., *Brit. med. J.*, 1959, **2**, 1041.

be confirmed only by direct measurement through a cardiac catheter.

The application of these and other tests has contributed greatly to our understanding of both normal and abnormal function. The doctor who carries them out on his patients soon recognizes the patterns of disorder which occur in various diseases. While it would not be practicable or desirable to apply these methods to every patient, there are several groups of patients in whom the tests may give information of crucial diagnostic and prognostic importance. Such an assessment is, for instance, of great value in examining a patient with diffuse pulmonary infiltration. It is almost essential in the investigation of the patient with breathlessness for which an adequate cause cannot be found and whom the physician may be tempted to label as hysterical. These tests are also invaluable in following the course of a disease and its response to treatment. For example, the treatment of the patient with emphysema and ventilatory failure can only be rationally conducted in the light of serial estimations of the tension of alveolar carbon dioxide. Attempts to determine the response to treatment with adrenal steroids of patients with a disease such as sarcoidosis are greatly aided by objective tests of function. It is clear that the search for a single test which will completely describe the abnormality of function will not be fruitful. However, the complexity of the tests used is more apparent than real when the subdivisions of the total function are considered and the tests selected accordingly. The continued application of these techniques must lead to a better understanding of lung disease and a more rational approach to its treatment.

ORAL TREATMENT OF TRICHOMONIASIS

It is well over a century since the flagellated protozoon, *Trichomonas vaginalis*, was discovered in a patient with vaginitis.[1] Much has since been learned about this infestation in humans, but several problems still remain unanswered.[2] When looked for as a routine the organism can also often be found in women during the years of sexual activity, though they may show no clinical evidence of vaginitis, and its presence in the male has recently received increasing attention. L. Watt and R. F. Jennison[3] found *T. vaginalis* in 18 (60%) of the husbands of 30 women suffering from trichomonal vaginitis, and there is now much evidence[4] to favour the view that trichomoniasis is most commonly transmitted by coitus. This epidemiological fact underlines the desirability of treating the male[5] as well as the infected female partner, and failure to do this has probably caused some "relapses" (really reinfections) in treated females in the past. While pessaries, insufflations, and douches remained the sole available means of treatment, results in the female were indifferent and no real attempt could be made to deal with infection in the male. Systemic treatment, preferably a drug given by mouth, was the obvious goal, but an earlier attempt to provide such a therapy (aminitrazole) ended in disappointment.[6-8]

Continued search for a remedy effective systemically led to experimental work[9] on metronidazole (1-β-hydroxyethyl-2-methyl-5-nitro-imidazole) and its first clinical trial[10 11] in France. Late in 1959 careful clinical trials of this drug ("flagyl") began in Britain, and preliminary reports of its effectiveness were communicated to the Medical Society for the Study of Venereal Diseases in London last May. The formal papers, subsequent discussion, and other complementary articles will appear in the September issue of the *British Journal of Venereal Diseases*.

Metronidazole is presented in tablets of 200 mg., and the usual dosage is one tablet thrice daily. P. Rodin *et al.*[12] prescribed 200 mg. by mouth thrice daily for seven days, without local treatment, in 82 women suffering from vaginal trichomoniasis. Immediate satisfactory responses occurred in 78 (95%). Of the 52 patients who attended for full assessment over a minimum period of three months, 3 failed to respond from the beginning, and 6 others relapsed or were reinfected. The cure rate at three months was therefore 43 out of 52 (83%). R. R. Willcox,[13] with similar dosage, had only 2 (5.9%) immediate failures in 34 patients, and 5 (14.7%) relapses during ninety days of post-treatment observation. Elsewhere in this issue of the *Journal* (p. 902) Drs. L. Watt and R. F. Jennison give a detailed report on 50 consecutive female patients also treated with metronidazole (200 mg. thrice daily for seven days); of 44 (88%) showing an immediate response, 25 (56.8%) remained free from infection for three months or longer, 29 (65.9%) for two months, and 39 (88.6%) for one month. C. S. Nicol *et al.*[14] treated 122 female patients with metronidazole (200 mg.

[1] Donné, A., *C.R. Acad. Sci. (Paris)*, 1836, **3**, 385.
[2] Editorial in *Brit. J. vener. Dis.*, 1960, **36**, 145.
[3] Watt, L., and Jennison, R. F., ibid., 1960, **36**, 163.
[4] Willcox, R. R., ibid., 1960, **36**, 167.
[5] King, A. J., in Report of Discussion, ibid., 1960, **36**, 161.
[6] Willcox, R. R., ibid., 1957, **33**, 115.
[7] Catterall, R. D., and Nicol, C. S., *Brit. med. J.*, 1957, **2**, 29.
[8] Dunlop, E. M. C., Philipp, E., and Watt, J. D., *Brit. J. vener. Dis.*, 1958, **34**, 57.
[9] Cosar, C., and Julou, L., *Ann. Inst. Pasteur*, 1959, **96**, 238.
[10] Durel, P., Roiron, V., Siboulet, A., and Borel, L. J., *C.R. Soc. franc. Gynéc.*, 1959, **29**, 36.
[11] —— *Brit. J. vener. Dis.*, 1960, **36**, 21.
[12] Rodin, P., King, A. J., Nicol, C. S., and Barrow, J., ibid., 1960, **36**, 147.
[13] Willcox, R. R., ibid., 1960, **36**, 175.
[14] Nicol, C. S., Barrow, J., and Redmond, A., ibid., 1960, **36**, 152.
[15] Durel, P., Couture, J., Collart, P., and Girot, C., ibid., 1960, **36**, 154.
[16] Whittington, M. J., ibid., 1957, **33**, 80.

thrice daily for only five days) with 5 (4%) immediate and 12 (10%) later failures, a success rate of 86%. Drs. Mary Moffett and M. Isabel McGill report at p. 910 in this issue their results with three different treatment regimes; using 200 mg. of metronidazole thrice daily for 10 days in 24 patients, they had no failures. Dr. Elisabeth Rees (p. 906) found that in 30 patients with clinical signs of *T. vaginalis* infestation and treated for seven days with 200 mg. of metronidazole thrice daily, 20 (67%) were clinically normal within seven days of the end of treatment, 8 (27%) were much improved, and 2 (6%) did not respond. All the above-mentioned studies have been most carefully carried out, with full microscopical and cultural control, and the results may perhaps be even better than the cautious claims suggest, since some at least of the relapses were probably reinfections rather than failures. Treatment during pregnancy has been equally effective, but metronidazole has no therapeutic effect on *Candida albicans*, the growth of which may even be encouraged.

So far trials of metronidazole in men have been limited, but the results tentatively suggest that it is equally effective. Rodin *et al.*[12] treated 20 men in whom *T. vaginalis* had been found. In 17 of these an active urethritis was present which quickly cleared in 13 of the patients: in the remaining 4 a local lesion (stricture, littritis, or prostatitis) was discovered. Nicol *et al.*[14] treated 11 men with no immediate or late failures. The preliminary clinical trials have not brought to light any serious side-effects, and the drug does not appear to change the blood picture in humans or to reduce fecundity in the rat.[15] Metronidazole (given orally) appears in the urine mostly in the free form[15]; this is of therapeutic significance, since *T. vaginalis* is known to occur in the urine in cases of vaginal trichomoniasis.[16]

These British studies show that metronidazole given by mouth in a dosage of 200 mg. thrice daily for seven days is effective in a high proportion of cases of human trichomoniasis in both sexes. The small number of immediate failures may be due to inability to absorb the drug, and in such female patients local vaginal treatment with metronidazole may then be needed. With this exception, however, local treatment seems no longer to be necessary. Further experience is required to confirm the initial observation that metronidazole is free from serious side-effects. The development and successful trials of this drug represent a major therapeutic advance which focuses attention on the need for better facilities for the diagnosis of trichomoniasis in both sexes. The temptation to treat vaginal discharge without investigation must be resisted, for other infections or pathological processes unresponsive to flagyl may be present. As infection is often transmitted sexually the male partner also requires examination and treatment. These developments clearly call for close co-operation between gynaecologist and venereologist. Many will wish to emulate the practice at St. Mary's Hospital for Women, Manchester, where the venereologist conducts special sessions for the treatment of trichomoniasis in women and for the investigation of their male partners in the gynaecological out-patient department.

CHLOROTHIAZIDE AND HYPERTENSION

Chlorothiazide was the first of the benzothiadiazine series of diuretic drugs to be used. Newer derivatives have a greater potency, which appears to result from increasing solubility in lipoids. The membrane of living cells consists mainly of lipoids, and substances of moderate molecular weight must have a high solubility in lipoids to traverse the cell membrane.[1] The increased potency of the newer derivatives of benzothiadiazine is no distinct advantage apart from the smaller doses being easier to take, but they may cause less depletion of potassium. All the derivatives have a similar hypotensive effect. E. D. Freis and I. M. Wilson[2] showed that chlorothiazide potentiates the action of other hypotensive drugs. Many other workers have also found that the dose of different hypotensive drugs can be reduced by the addition of chlorothiazide. This diuretic is also effective in lowering the blood-pressure of patients who have had dorso-lumbar sympathectomy.[3] Chlorothiazide alone may cause some reduction in blood-pressure. D. Stuckey[4] found that the blood-pressure fell in one out of twenty hypertensive patients treated with chlorothiazide only. If the drug initially produces a hypotensive effect, it is unusual for this to persist. When this diuretic is combined wih a ganglion-blocking drug or the newer agents which selectively paralyse adrenergic neurones, excessive hypotension is readily induced.[5] Unfortunately there is still a tendency for tolerance to develop.

How these diuretic drugs exert a hypotensive effect and more particularly how they enhance other hypotensive drugs is not clear. It has been shown[6] that a diminution in plasma volume occurred with chlorothiazide at the same time that sensitivity to pentolinium increased. Replacement of the lost plasma volume with salt-free dextran abolished this effect. A. Wanko and Freis[7] showed that chlorothiazide reduces the pressor effect of noradrenaline and also attributed this to a reduction in plasma volume. Polish workers[8 9] have confirmed this work on the influence of chlorothiazide on the pressor response to noradrenaline in

[1] Milne, M. D., *J. Irish med. Ass.*, 1960, **46**, 66.
[2] Freis, E. D., and Wilson, I. M., *Med. Ann. Distr. Columbia*, 1957, **26**, 468.
[3] Wilkins, R. W., *J. Amer. med. Ass.*, 1958, **167**, 801.
[4] Stuckey, D., *Med. J. Aust.*, 1959, **11**, 349.
[5] Nash, J., *J. Irish med. Ass.*, 1960, **46**, 70.
[6] Dollery, C. T., Harington, M., and Kaufmann, G., *Lancet*, 1959, **1**, 1215.
[7] Wanko, A., and Freis, E. D., *Circulation (N.Y.)*, 1958, **18**, 792.
[8] Aleksandrow, D., Wysznacka, W., and Gajewski, J., *New Engl. J. Med.*, 1959, **260**, 51.
[9] —— ibid., 1959, **261**, 1052.
[10] Wilson, I. M., and Freis, E. D., *Circulation (N.Y.)*, 1959, **20**, 1028.
[11] Tobian, L., *Circulat. Res.*, 1956, **4**, 671.

hypertension. But they failed to find any changes in the circulatory blood volume, and believe that the fall in blood-pressure in patients receiving chlorothiazide results from a lowering of peripheral resistance without reduction in cardiac output. Wilson and Freis[10] agree that the late hypotensive effect of chlorothiazide cannot be due to reduction of blood volume. They have found that the blood volume after a year has returned to normal in patients whose blood-pressure remained lowered by chlorothiazide. L. Tobian[11] has suggested that in hypertension the inner part of the arteriolar wall is thickened with oedema due to retention of sodium, and that this is corrected by the diuretic. Alternatively, it has been suggested[9] that reduction of intracellular sodium may lower the arteriolar tone.

In contrast to its potentiation of ganglion-blocking drugs, chlorothiazide alone is not usually an effective hypotensive agent. It appears that the enhancement produced by the diuretics is due in the first place to a reduction of plasma volume. Reduction in plasma volume causes an increased vasomotor tone. The increased tone is susceptible to the ganglion-blocking drugs or the newer selective adrenergic-blocking agents such as bretylium tosylate.

At a conference held by the New York Academy of Sciences on new diuretics and anti-hypertensive agents in May of this year, all participants said that they started treatment of mild hypertension with a diuretic. Only one member disagreed with the statement that all persons with a blood-pressure of more than 150/90 mm. Hg required some treatment with a diuretic. In Great Britain it is doubtful whether the most ardent advocates of reducing blood-pressure would subscribe to this view. Besides the variable course of benign hypertension and the questionable value of reducing blood-pressure in mild cases, the long-term toxic effects of chlorothiazide and allied drugs have yet to be fully assessed. When hypertensive disease is present and reduction of blood-pressure is warranted on rigid criteria, which take into account the state of the retina, heart, brain, and kidneys, the combination of a benzothiadiazine drug with other hypotensive agents is justifiable.

CONTROL OF COMMUNICABLE DISEASES

The handbook on the control of communicable diseases in man, published by the American Public Health Association, provides an example of the value of international co-operation. This handbook has come to be recognized in Great Britain as an authoritative source of information on the epidemiology and prevention of infectious diseases, and its value here has been enhanced by the fact that in the preparation of the last four editions representatives from Britain have collaborated with the editorial committee. In the text there are frequent references to British practice where this differs from that in the United States.

The ninth edition has just been published.[1] In general form it follows the lines of its predecessors. After the preface and a section on definitions (both of which deserve more than passing notice) a chapter on each disease follows in alphabetical order. The arrangement of each chapter follows the well-known form of previous editions and provides sections on occurrence, infectious agent, reservoir and source of infection, mode of transmission, incubation period, period of communicability, susceptibility and resistance, and methods of control.

Some of the chapters have been rewritten. It is interesting to see that, though reference is made to the fact that live poliomyelitis vaccines are being evaluated, the formalinized vaccine is recommended, a fourth dose being given a year or more after the third. Somewhat surprisingly, the authors state that immunization against poliomyelitis can begin at the age of 2 months. A significant addition to the chapter on influenza stresses the importance of attempting to mobilize facilities for development and production so as to permit rapid shipment and use of the appropriate vaccine when a new strain appears.

A new chapter on arthropod-borne viral infections considerably increases the value of the book, but workers in Great Britain will be more interested in such new chapters as those on aseptic meningitis, salmonellosis, staphylococcal infections, and acute diseases of the upper respiratory tract. The upper respiratory infections are considered under four headings, pharyngo-conjunctival fever, acute respiratory disease of military recruits (both of which are associated with adenoviruses), acute respiratory diseases of unknown aetiology, and the common cold. Aseptic meningitis may be caused by a wide variety of viruses, the commonest being those of group-B Coxsackie, mumps, E.C.H.O., and lymphocytic choriomeningitis, and improved virological techniques have allowed an increasing number of such cases to be differentiated from similar cases caused by poliomyelitis virus. It is not surprising to find that the present edition has a new chapter on staphylococcal infections—the first part on impetigo contagiosa and the second on the general infections. The importance of general infections with the staphylococcus and knowledge of their aetiology have both grown so much in recent years that this summary of the main principles of prevention and control will be helpful.

[1] *Control of Communicable Diseases in Man*. 1960. American Public Health Association, N.Y.

ELECTROMAGNETIC HEATING OF MALIGNANT GROWTHS

"Diseases that the knife does not cure are cured by fire." This famous judgment of Hippocrates is still appropriate in the treatment of cancer, where the subtle fire of the radiotherapist is the best alternative (or adjunct) to the surgeon's knife. In seeking further refinement of their electromagnetic cautery, the radiotherapists have made important technical advances during the last three decades. Accurate systems of dosage for *x* rays and radium were developed during the 1930's. Improvements in penetrating power have been obtained by the vigorous exploitation of new high-voltage generators designed originally for research in nuclear physics.

[1] d'Arsonval, A., and Charrin, A., *C.R. Soc. Biol. (Paris)*, 1893, **5**, 467.
[2] Gossett, A., Gutmann, A., Lakhovsky, G., and Magrow, J., ibid., 1924, **91**, 626.
[3] Schereschewsky, J. W., *Publ. Hlth Rep. (Wash.)*, 1926, **41**, 1939.
[4] Gilchrist, R. K., *Surg. Gynec. Obstet.*, 1960, **110**, 499.

When these powers are fully used there remains one formidable obstacle—the difficulty of obtaining any substantial difference in sensitivity between the malignant cells and the surrounding healthy tissue through which the therapeutic rays must pass. Efforts to modify radiosensitivity by drug action have had limited success. Early hopes that radioactive isotopes might be made to concentrate in tumours have not been fulfilled.

The selective biological action of currents induced by diathermy has long been a topic for speculation and experiment. Bactericidal effects were reported by A. d'Arsonval and A. Charrin[1] as long ago as 1893. Regression of tumours in plants and animals were first reported[2 3] more than thirty years ago. Such claims are now discredited, the effects being attributed merely to incidental heating. Suggestions for further research have recently been made by R. K. Gilchrist,[4] of Chicago. Noting that many organisms have little tolerance to temperature changes, he proposes that the heat generated by external electromagnetic fields might be used to destroy tumours. Local necrosis has been demonstrated in animal tissues infiltrated with tiny particles of iron or other magnetic materials. Here the action of the electromagnetic field is to produce heating by hysteresis—a kind of magnetic inertia. When no magnetic targets are present, the heating effects are less pronounced; they are also influenced by the depth, vascularity, and electrical properties of the tissues in the field. Gilchrist outlines three possibilities which must, in the present state of knowledge, be regarded as highly optimistic. The first is the elevation of temperature in particular organs or tissues by specially constructed diathermy coils energized at appropriate frequencies. This is a task to daunt the boldest electronic engineer, and it is not to be expected that the ultimate degree of localization will be better than that now possible with sharply defined *x*-ray beams. Secondly, it is hoped that the malignant cell might succumb to heat "since it is accustomed to growing in a very restricted thermal environment." Thirdly, it is thought likely that the temperature effect can be enhanced by the systemic use of hormones, enzymes, or cytotoxic drugs. These are far-fetched ideas. Radiotherapists would be the first to concede the limitations of their methods and to encourage any new approach to the treatment of cancer on rational lines, but they are not likely to feel that diathermy has anything useful to offer them at present.

QUESTIONING THE ANSWERS

Any one observer using a measuring device will rarely succeed in reproducing the same measurement in two successive observations of the same object. This variability may be reduced by care and skill in the design and operation of the measuring device, but in some degree it is inescapable. This has been recognized and accepted for centuries in the physical sciences. In schools to-day quite young children using, for example, spherometers, are taught to average several readings and to aim at reducing their range. But in clinical medicine the existence of variability in observations is hardly yet so fully accepted. While medical men have long agreed that a "second opinion" can exist about diagnosis—that is, about the interpretation of abnormalities—they have been tardy in acknowledging that there could be different assessments of abnormalities in a patient, or of what constitutes the normal range of variation.

But in the last ten or so years various investigators have shown a substantial lack of agreement between observers independently examining the same patients or the same radiographs, and also in assessments of nutritional state, body measurements, Mantoux tests, selection for tonsillectomy, and the detection of pulmonary emphysema, the third heart sound, and enlargement of the liver. Serial investigations do not entirely eliminate variability but they do reduce it. There is one field of medicine of growing importance—namely, epidemiology—in which this safeguard sometimes does not operate. This is when a team of interviewers ascertains the answers to questions at a single interview with members of the population sample being studied. Such an inquiry can give unreliable results owing to observer variability.

The extent of this variability in the completion of questionaries was clearly demonstrated by A. L. Cochrane[1] and his colleagues in 1951. Several medical observers interviewed groups of coal miners of similar age distribution using the same questions to elicit medical history. The results showed that observer bias was influencing the frequency of a positive answer to a question. In 1955 R. S. F. Schilling and his team[2] reported the results of independent examination by two medical workers of a group of cotton workers to assess the reliability of diagnosing byssinosis, eliciting certain clinical signs of respiratory disease, measuring chest expansion and recording blood-pressures, and taking histories of certain respiratory symptoms. There was significant disagreement between the observers in recording absent apical impulse, movement of chest, kyphosis, and cyanosis, and in the measurement of chest expansion and blood-pressure. There was observer bias both in finding abnormality and in history taking.

More recently A. S. Fairbairn and colleagues[3] have reported an investigation in which three doctors and three health visitors obtained, in interview, answers to a questionary on respiratory symptoms, each subject being examined twice. They, too, found much evidence of observer bias. This report makes a number of advances on earlier work. Apart from showing, more clearly than before, the hazards of interviewer bias, Fairbairn and his colleagues, as a result of the careful and thorough design of their survey, were able to show the nature and sources of disagreement and to make useful suggestions about future interview procedure, especially in regard to the design of the questionary and the drafting of instructions to interviewers.

We record with regret the death on September 16 of Air Marshal Sir Victor Richardson, Director-General of Medical Services, Air Ministry, from 1938 to 1941.

[1] Cochrane, A. L., Chapman, P. J., and Oldham, P. D., *Lancet*, 1951, 1, 1007.
[2] Schilling, R. S. F., Hughes, J. P. W., and Dingwall-Fordyce, I., *Brit. med. J.*, 1955, 1, 65.
[3] Fairbairn, A. S., Wood, C. H., and Fletcher, C. M., *Brit. J. prev. soc. Med.*, 1959, 13, 175.

Clinicopathological Conference

AN OBSCURE CASE

DEMONSTRATED AT THE
POSTGRADUATE MEDICAL SCHOOL OF LONDON

This is a puzzling case featuring haemolytic anaemia, an acute polyarthritis, an aortic valve lesion, and pulmonary hypertension (Case No. 164,666; P.M. No. 8,557). The patient was treated at Hammersmith Hospital.

Clinical History

Dr. J. F. GOODWIN: This patient was a woman aged 61 years at the time of her death in 1958. She was first seen in 1950, when she complained of loss of weight, sweating, unsteadiness of her legs, and dark urine. She had suffered concussion in 1919, and jaundice in 1949. Following the concussion she complained of headaches and vertigo, and had a mild left hemiparesis.

On examination she was a thin, anxious woman, with slight icterus. The liver and spleen were enlarged, the latter greatly so. There were no signs of hepatic failure. The lymph nodes were not enlarged. An ejection systolic murmur of moderate intensity, followed by an early diastolic murmur, was heard at the left sternal border; the second heart sound was normal, as were the cardiac impulse and jugular venous pulse. The blood-pressure was 145/75 mm. Hg. There was a left hemiparesis, with "glove and stocking" anaesthesia, and loss of taste.

Urine.—Excess of urobilinogen; no bilirubin, porphyrins, or haemoglobin. *Blood* (*see Table*).—W.R. and Kahn tests positive; urea 28 mg./100 ml.; E.S.R. 105 mm./1 hr.; thymol turbidity 17; colloidal gold 4; bilirubin 1.5 mg./100 ml.; cholesterol 182 mg./100 ml.; protein 6.9 g./100 ml.; albumin/globulin ratio 3.4/3.5; Hb 65%; reticulocytes 4%; W.B.C. 4,400–3,300/c.mm. (lymphocytes 45%). Direct Coombs test positive; platelets 67,000–21,000/c.mm.; cold agglutinins (1:1,000 dilution) positive.

Radiology.—Left ventricle enlarged; aorta dilated; no calcification seen. Lungs clear (Fig. 2). Intravenous pyelography normal. *Cardiogram.—Normal* (Fig. 1, 5/8/1950). *C.S.F.*—Normal. *Sternal Marrow.*—Average cellularity; increased lymphocytes.

The diagnosis was considered to be an acquired haemolytic anaemia with hypersplenism. The positive serological findings were thought to be due to the anaemia, but cardiovascular and cerebrovascular lues were not completely excluded. Aortic incompetence was present, but the cause was uncertain, and it might have been due to syphilis. Hysterical traits were noted as features of her personality.

A course of antisyphilitic treatment with iodides, bismuth, and penicillin was given, and splenectomy was then performed. Histological examination of the spleen revealed increased blood in the pulp, dilated sinuses, and hyperplastic Malpighian bodies. There was little iron. The appearances were consistent with haemolytic anaemia. After operation the abnormal haematological findings disappeared, the platelets rising to 280,000/c.mm., the haemoglobin to 96%, and the white blood cells to 7,000/c.mm. The serum bilirubin fell to 0.7 mg./100 ml.

ACUTE POLYARTHRITIS

The patient remained well until 1954, when she was admitted in July with acute polyarthritis of recent onset, involving the small joints of the hands and the shoulders, resembling acute rheumatoid arthritis. The other physical signs were unaltered, except that the arterial pulse had assumed a bisferious quality suggesting an increase in the degree of aortic stenosis and incompetence. The blood-pressure was 155/90 mm. Hg.

Urine.—Normal. *Blood* (*see Table*).—E.S.R. 50 mm./1 hr.; Hb 79%; reticulocytes 3%, 6%; W.B.C. 5,000/c.mm.; antistreptolysin titre 100 units; W.R. and Kahn negative; lupus erythematosus cells not found; proteins 7.7 g./100 ml.; albumin/globulin ratio 4.4/3.3; urea 26 mg./100 ml.

A diagnosis of acute rheumatoid arthritis was made, and disseminated lupus erythematosus was considered likely. The patient improved with rest, physiotherapy, and salicylates. The arthritis resolved completely.

PULMONARY HYPERTENSION

In March, 1955, she was readmitted complaining of cough, dyspnoea, substernal pain on exertion, with

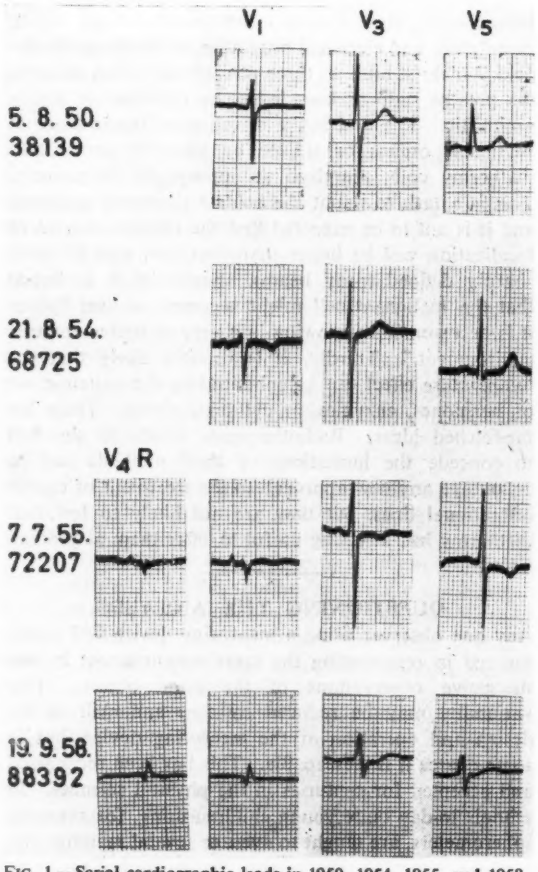

FIG. 1.—Serial cardiographic leads in 1950, 1954, 1955, and 1958. The development of a dominant R wave in lead V_4R and V_1 and the deep S wave in V_5 with T-wave inversion indicate progressive right ventricular dominance.

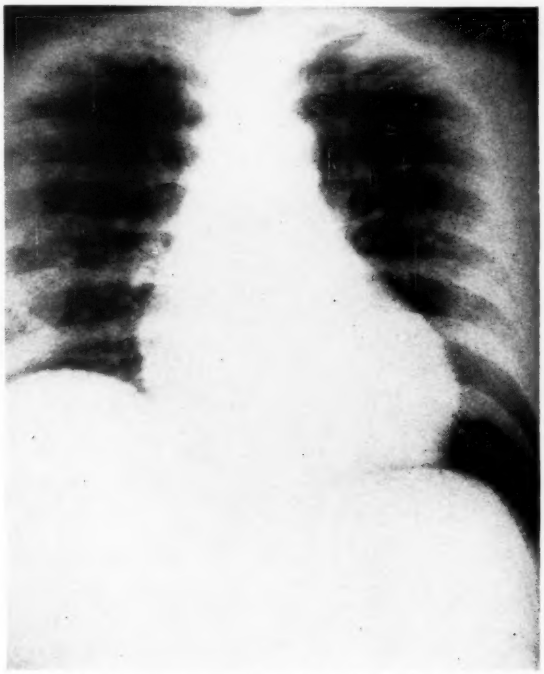

FIG. 2.—Six-foot postero-anterior radiograph of the chest in 1950, showing enlargement of the aorta.

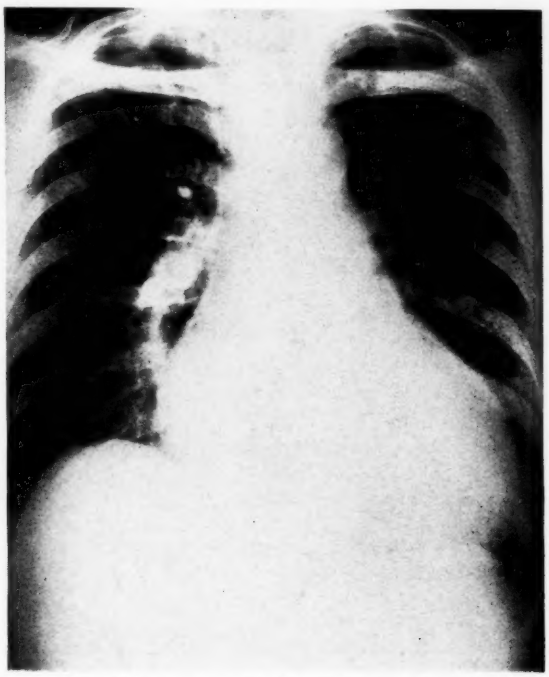

FIG. 3(*a*).—Six-foot postero-anterior radiograph of the chest in 1955, showing enlargement of the right ventricle and of main and large pulmonary arteries, with clear peripheral lung fields characteristic of obliterative pulmonary hypertension.

FIG. 3(*b*).—Left lateral film showing enlargement of both ventricles but not of the left atrium.

FIG. 4.—Six-foot postero-anterior chest radiograph in 1958, showing further enlargement of the main pulmonary artery and greater clarity of the peripheral lung fields.

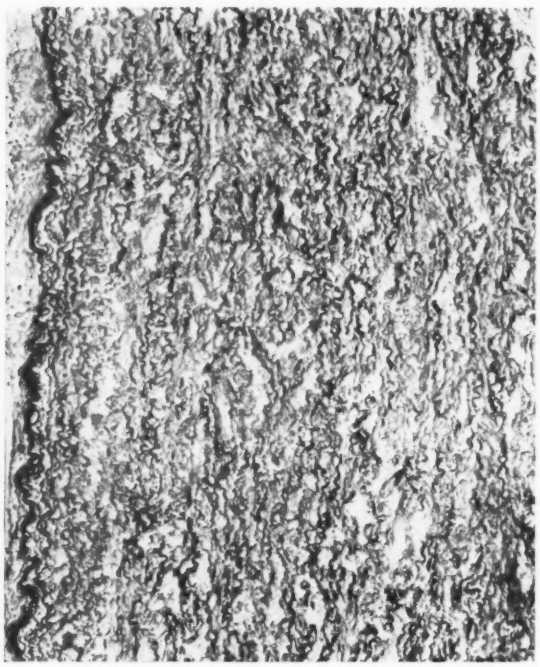

FIG. 6.—Main pulmonary artery, showing the irregular pattern of the elastic tissue in acquired hypertrophy. (×111. Elastic stain showing elastic fibres in black.)

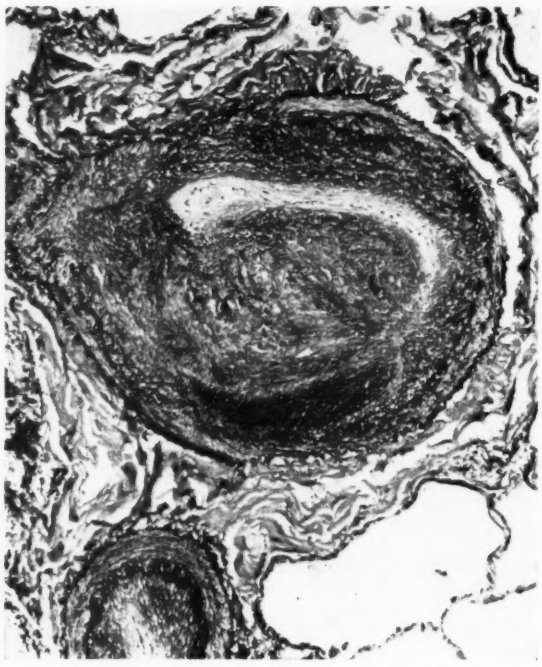

FIG. 7.—Muscular pulmonary artery virtually occluded by organized embolus. The lumen is visible as a pale, narrow slit. The media has been destroyed at some points. An adjacent branch shows concentric intimal thickening. (×108.)

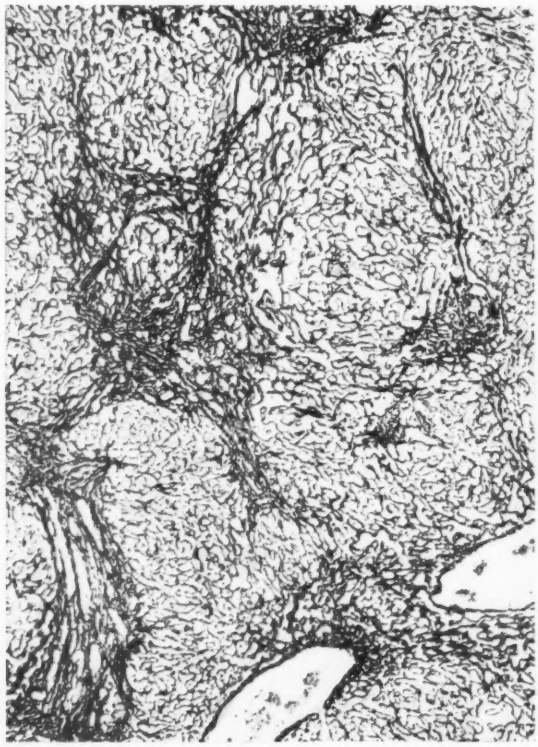

FIG. 8.—Cardiac cirrhosis of the liver. Silver-impregnated section showing loss of lobular pattern and foci of reticulin fibrosis. The latter involve both portal and central areas. (×52.5.)

FIG. 9.—Kidney, showing abscess. (×52.5.)

tiredness and giddiness for four months. On examination, signs of pulmonary hypertension were now evident: the right ventricle was enlarged and the jugular venous pressure showed an augmented "a" wave 3 cm. above the sternal angle. An atrial sound was audible, and the second heart sound was narrowly split, with accentuation of pulmonary closure. The previous murmurs were unchanged, and no mitral diastolic murmur was heard on repeated examination. There was slight clubbing of the fingers and toes, and the blood-pressure was 190/110 mm. Hg. The lungs were clear. The optic fundi were normal.

Urine.—Esch. coli; albumin 50 mg./100 ml. *Blood (see Table).*—Hb 99%; W.B.C. 5,000/c.mm.; platelets 180,000/c.mm.; Coombs test positive; W.R. negative; urea 23 mg./100 ml.; bilirubin 1 mg./100 ml.; cultures negative; red-cell survival time, half normal.

Radiology.—Pulmonary artery now enlarged, with small peripheral branches, characteristic of obliterative pulmonary hypertension. Ventricles enlarged; right atrium prominent; left atrium not enlarged; no pulmonary venous hypertension; no mitral or aortic valve calcification. Lungs clear. (Figs. 3 (*a*) and (*b*)). *Cardiogram.*—Deep S wave in V_5, with T-wave inversion in V_3 and V_5, indicating right ventricular enlargement. P waves normal (Fig. 1, 7/7/1955).

A diagnosis of obliterative pulmonary hypertension was made, vasoconstrictive and hyperdynamic hypertension having been excluded. Especial care was taken to exclude the presence of extreme mitral stenosis with resultant vasoconstriction in the pulmonary arteriolar bed. No evidence of pulmonary venous hypertension, intracardiac shunt, or of lung disease was forthcoming, and it was concluded that the pulmonary hypertension was due to obliteration of the pulmonary arteriolar bed by occlusive disease. It was thought that such disease was due to an arteriolitis resulting from the same process which had caused the haemolytic anaemia, aortic valve disease, and polyarthritis. Disseminated lupus erythematosus was then considered very probable, and the rise in systemic blood-pressure was considered to favour this.

In view of the patient's lability of mood and depressive tendency, permanent adrenal-steroid therapy was not considered advisable, and she was maintained on digitalis, with some improvement.

Congestive Failure

In July, 1956, she was again readmitted with signs of right-ventricular congestive failure. Her dyspnoea had increased, and cyanosis was now visible. The "a" wave of the jugular venous pressure was now 10 mm. above the sternal angle, and a pulmonary systolic click was heard. The liver was enlarged and pulsated in late diastole.

Cardiogram.—Increasing right ventricular hypertrophy. *Cardiac Catheterization.*—Pulmonary-artery pressure 70/35 mm. Hg; right-ventricular pressure 70/15 mm. Hg; cardiac output 3.0 litres/min.; arterial oxygen-saturation 92%; pulmonary vascular-resistance 13 units. No left to right shunt.

The pulmonary vascular-resistance decreased from 13 to 9 units after hexamethonium, but the systemic resistance fell also. These findings confirmed the presence of obliterative pulmonary hypertension.

Treatment with cortisone, digitalis, diuretics, and a low-salt diet was given, but the patient subsequently developed an attack of faintness, dyspnoea, and haemoptysis, with a fall in blood-pressure and a rise in jugular venous pressure. A pulmonary artery thrombosis was diagnosed (Ball *et al.*, 1956) and treatment was started with anticoagulants. Treatment with cortisone did not appear to exert any beneficial effect and was stopped. The patient improved slowly, but remained greatly limited. The possibility of recurrent silent pulmonary micro-emboli (McMichael, 1948: Owen *et al.*, 1953) was considered, but rejected in favour of pulmonary thrombosis secondary to occlusive pulmonary arteriolitis, pulmonary hypertension, and heart failure. In view of the patient's temperament and previous blood disorder, anticoagulants were not continued on a permanent out-patient basis. An attempt was made to dilate the pulmonary vascular bed with dibenylene, and with aminophylline derivatives, but without obvious clinical effect. Ganglion-blocking agents were not used because of the danger of reducing cardiac output (Goodwin *et al.*, 1958).

Terminal Illness

The patient was maintained in poor health with digitalis, diuretics, and a low-salt diet, but was readmitted in September, 1958, because of an increase in dyspnoea, development of oedema, and dysuria. She was then very ill, being weak, drowsy, and cyanosed. The jugular venous pressure was now 12 mm. above the sternal angle and atrial fibrillation had developed. The blood-pressure was 105/80 mm. Hg and there was extensive oedema.

Urine.—Esch. coli; pus cells. *Blood (see Table).*—Urea 84 mg./100 ml.; Hb 84%, falling to 58%; platelets 48,000/c.mm.; E.S.R. 90 mm./1 hr.; cold agglutinins 1/256 at 40° C. *Bone-marrow.*—Hypoplastic; lymphocytic infiltration.

Radiology.—Further enlargement of the pulmonary artery (Fig. 4). *Cardiogram.*—Dominant R wave in V_4R and V_1, indicating increased right ventricular enlargement (Fig. 1, 19/9/1958).

The oedema decreased with diuretics and the urinary infection resolved with nitrofurantoin. Prednisolone

Results of Serial Investigations of the Blood

	Hb (%)	W.B.C. (c.mm.)	Platelets (c.mm.)	E.S.R. (mm. hr.)	Urea (mg.%)	Bilirubin (mg.%)	Alb. (g.%)	Glob. (g.%)	W.R.
1950—Pre-operative	65	3,300 4,400	50,000 67,000 21,000	105	28	1·5	3·4	3·5	Pos.
1950—Post-operative	90	7,000	280,000	—	—	0·7	4·4	3·9	,,
1954—Arthritis	79	5,500	190,000	45 50	26	1·3	4·4	3·3	Neg.
1955	99	5,000	180,000	27	23	1·0	3·5	3·5	,,
1956	108	3,000	—	52	32	—	4·1	3·6	—
1958—Terminal congestive heart failure and renal infection	84 58	5,000	48,000	90	84	2·2	3·4	3·5	Neg.

was given, but without effect. Blood cultures were taken after a rigor and revealed *Pseudomonas pyocyanea*. Before treatment could be instituted, the patient died suddenly.

Clinical Diagnosis

(1) "Collagen" or auto-immune disease, probably disseminated lupus, causing haemolytic anaemia, polyarthritis, aortic valve disease, and pulmonary arteriolitis.

(2) Obliterative pulmonary hypertension leading to right ventricular failure.

(3) Renal infection and terminal septicaemia.

Post-mortem Findings

Professor C. V. HARRISON: The body was that of an ill-nourished, elderly-looking woman, with oedema of lower limbs and back, a well-healed splenectomy scar, and an old, just visible, suprapubic scar of a ventrofixation.

Heart 370 g. (N=270 g.). The right atrium was moderately hypertrophied. The tricuspid valve was dilated and appeared functionally incompetent. The right ventricle was hypertrophied to 6 mm. in the conus. The right ventricular hypertrophy was confirmed histologically. At the apex there was a fibrin thrombus (Fig. 5) firmly attached to the wall but not apparently endothelialized. Histologically the right ventricular thrombus showed long-standing fibrous organization at its attachment. The left atrium was normal. The mitral valve showed some thickening of its aortic cusp, and slight fibrosis was confirmed histologically. The left ventricle was not hypertrophied. The aortic valve showed much old fibrosis and fusion of two commissures, only the commissure between the left coronary and non-coronary cusps being normal. There was thickening of the valve curtains and a little calcification. There was a terminal vegetation on the non-coronary cusp. The coronary arteries showed mild atheroma but without serious narrowing. The myocardium of the left ventricle showed numerous small foci of fibrosis. *Aorta*.—The first part was normal and there was only moderate atheroma in the rest. Microscopically there was no sign of syphilis. The *pulmonary artery* (Figs. 6 and 7) showed the acquired type of hypertrophy described by Heath *et al.* (1959). *Lungs* were of normal weight and appeared healthy externally. After injection, the pulmonary arteries showed a normal vascular pattern proximally, but narrowing distally, there being hardly any filling in vessels beyond the elastic arteries. Pleurae were normal. Sections showed that innumerable small pulmonary arteries were partially occluded. These were muscular arteries or sometimes arterioles. The occlusions were fibrous and often there were multiple lumina. Proximal to the occlusions there was hypertrophy, but this was irregular and not severe. The lung parenchyma appeared healthy. The appearances were typical of embolic pulmonary hypertension.

The *alimentary tract* was healthy. *Liver* was of normal weight, but showed a fine granularity externally. The cut surface showed "cardiac cirrhosis" (Fig. 8), with dark congested areas alternating with pale areas of regeneration in a leaf-like pattern. Sections confirmed this and showed extensive fibrosis around central veins, sometimes joining up with portal tracts. The *spleen* had been removed, but histological sections of it were available. Spleen at operation weighed 1,375 g. (N=150 g.). It showed a dark red pulp with prominent Malpighian bodies. Microscopically the splenic sinu-

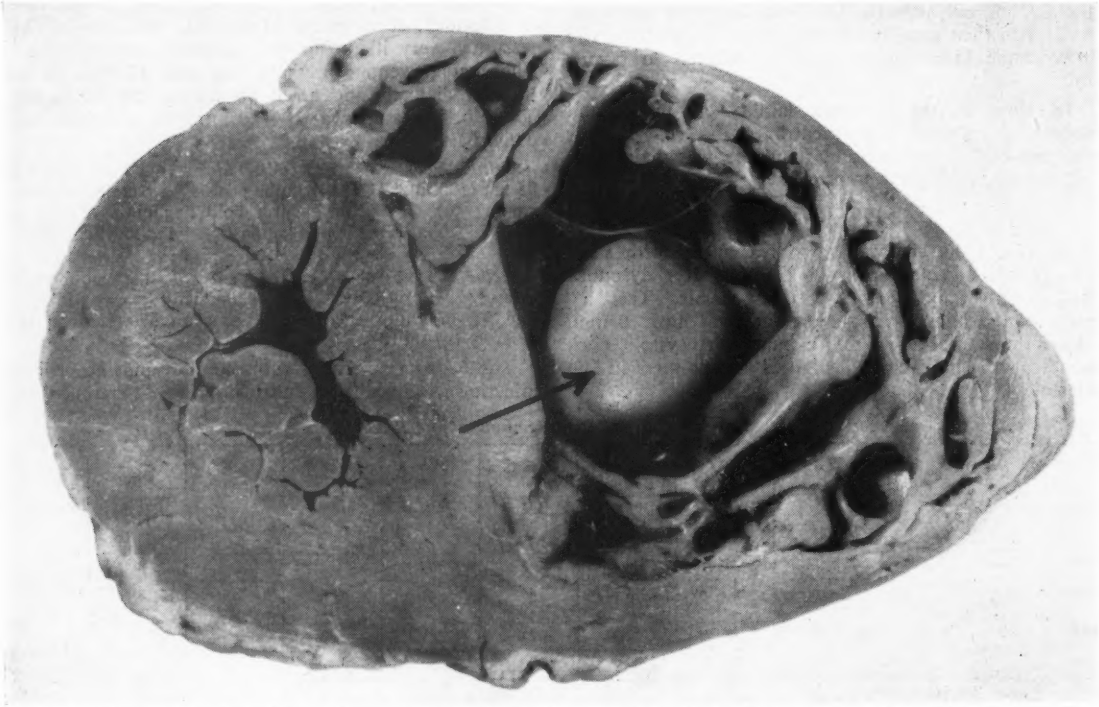

FIG. 5.—Cross-section of ventricles to show a thrombus (indicated by arrow) attached at the apex of the right ventricle. Note the remarkable hypertrophy of the right ventricle. (×1.7.)

soids were enlarged and prominent and had swollen lining littoral cells. There was some erythrophagocytosis. Malpighian bodies were unduly prominent for the patient's age, and showed active germinal centres. The appearances were consistent with an acquired haemolytic anaemia. *Lymph nodes* showed a little generalized enlargement, but they were not microscopically abnormal. *Bone-marrow.*—In the spine, sternum, and ribs the marrow was macroscopically about one-quarter yellow and three-quarters red. Microscopically the vast bulk of the marrow was fatty, though qualitatively it appeared normal. The general picture was one of hypoplasia.

The *right kidney* (145 g.) appeared healthy. In the *left kidney* (165 g.) in the postero-lateral part near the middle there was an area 13 by 20 by 15 mm. consisting of multiple coalescing abscesses. This lesion was strictly localized just under the capsule and there was no diffuse pyelonephritis in either kidney. Microscopically (Fig. 9) there were numerous recent coalescing abscesses with relatively infrequent Gram-negative bacilli. *Uterus* showed an old ventrofixation. In the anterior lip of the cervix there was a roughened friable area 2 cm. in diameter. Section of this showed an intra-epidermal carcinoma in some parts and ordinary infiltrating carcinoma in other parts. The rest of the uterus, tubes, and ovaries were normal. *Central nervous system* could not be examined. Other organs appeared healthy.

Pathologist's Diagnosis

(1) Splenectomy (1950) for acquired haemolytic anaemia.

(2) Thrombus in right ventricle.

(3) Old rheumatic aortic sclerosis with mild stenosis.

(4) Multiple minute pulmonary emboli producing obstructive pulmonary hypertension.

(5) Right ventricular hypertrophy.

(6) Multifocal myocardial fibrosis.

(7) Blood-borne abscess of left kidney.

(8) Carcinoma of uterine cervix.

(9) Old ventrofixation of uterus.

Discussion

Professor J. V. DACIE: Perhaps I may say a brief word about the haemolytic anaemia. She had haemolytic anaemia of a most unusual type. It was associated with the formation of cold antibodies of high thermal amplitude acting in the laboratory up to a temperature of about 30° C. This would be an unusual type of acquired haemolytic anaemia to be found in association with disseminated lupus. Normally, the antibodies in that disorder are of the so-called warm type, active at 37° C. The present patient's serology was studied intensively by Dr. de Gruchy and myself nine years ago. We found she had in her serum two antibodies: a cold agglutinin at a titre of approximately 1,000 and a haemolytic factor which would haemolyse normal red cells when they were treated with the enzyme trypsin.

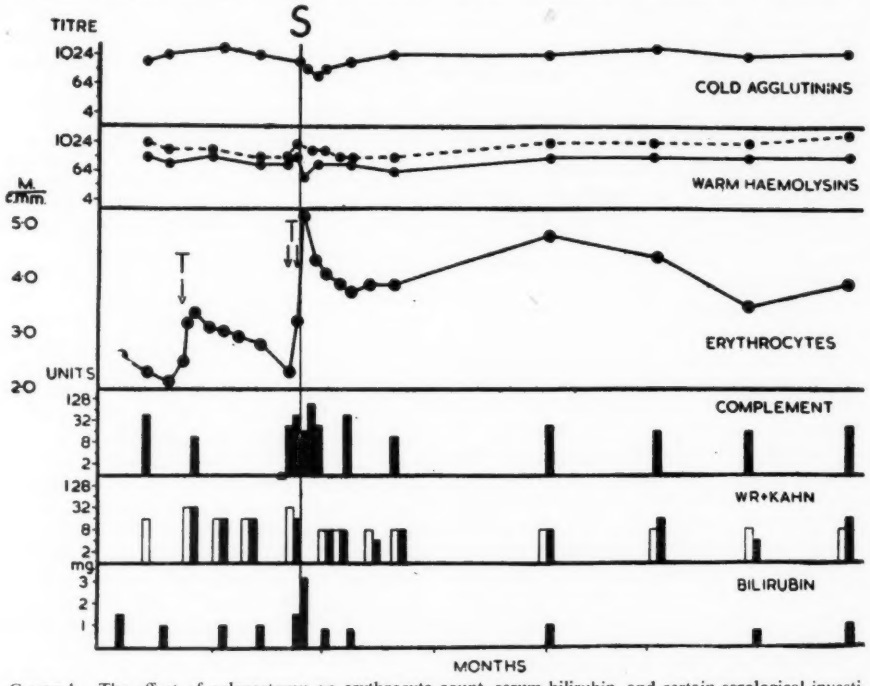

CHART 1.—The effect of splenectomy on erythrocyte count, serum bilirubin, and certain serological investigations. "S" denotes splenectomy.

EFFECT OF SPLENECTOMY

Chart 1 illustrates the effect of splenectomy. The red-cell count was falling and was only temporarily raised by transfusion. Splenectomy was carried out and after an initial fall she maintained her red-cell count fairly well between 3.5 and 4.5 millions per c.mm. without further transfusions. Before splenectomy the serum bilirubin was mostly above 1 mg. per 100 ml.; serum from the splenic vein contained 3 mg., which pointed to the spleen as a site of red-cell destruction. After splenectomy the bilirubin values fell slightly. The cold agglutinin and haemolytic factor titres were not altered by splenectomy. This is a common finding in acquired haemolytic

anaemia, for antibody formation seems hardly altered by splenectomy. Another feature was a low level of serum complement. This is quite commonly found in cold-antibody-type haemolytic anaemia, but also, I believe, sometimes in disseminated lupus. Quantitative estimations on her Kahn and Wassermann reactions showed that these, too, were not substantially altered by splenectomy. Chart 2 shows observations on red-cell survival, measured by the Ashby method, before and after operation. After splenectomy there was a substantial improvement, and I think this improvement was enough for her to maintain equilibrium between red-cell formation and destruction. The improvement in cell-survival suggested that the spleen was playing an important part in haemolysis.

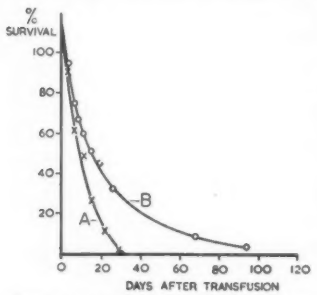

CHART 2.—The effect of splenectomy on the survival of group O N normal erythrocytes transfused to the patient: (A) before splenectomy, (B) after splenectomy. The survival studies were carried out by Ashby's method using potent anti-M agglutinating serum.

Professor J. MCMICHAEL: Dr. Goodwin, would you like to crystallize out of this a bit?

Dr. GOODWIN: I'll try, Sir, but it's extremely difficult. This patient, of course, presented considerable problems in diagnosis and management and we went through a number of phases in diagnosis. I tried very hard to persuade myself and others that she really had systemic lupus, because it seemed to me that it would fit better than anything else. I would like to know from the experts more about this haemolytic anaemia. What was it due to? Was there some underlying disease, and, if not, why did she have this rheumatoid arthritis, and why did some of the evidence of an auto-immune process apparently crop up again in the terminal phase? Was that all due to her heart failure? These are questions that I can't answer and I should like somebody else to answer them for me.

OBLITERATIVE PULMONARY HYPERTENSION

From the cardiac point of view I think there are one or two points worth making. The diagnosis of the type of disturbance of function in her circulation wasn't really very difficult. She developed the characteristic signs of obliterative pulmonary hypertension. But then I think that I went a little bit off the rails because I persuaded myself that her pulmonary vessels must be blocked by a specific arteritis, or something of that sort, and that thrombosis was a secondary phenomenon, for our only clinical evidence of pulmonary thrombosis came after she had developed signs of pulmonary hypertension. I have been looking up the evidence for arteritis causing obliterative pulmonary hypertension, and I must say it seems to me to be awfully thin. Involvement of the heart and lungs in polyarteritis, for instance, doesn't really include this at all. You can get coronary artery aneurysms and cardiac infarction; you can get a cardiomyopathy, and you can get classical pulmonary polyarteritis with migrating shadows, eosinophilia, and wheezing; but blockage of pulmonary vessels just doesn't seem to occur. In a recent review on the heart in systemic lupus, Shearn (1959) cites one patient said to have pulmonary hypertension, but none with right-sided heart failure as a result of pulmonary vascular obstruction. So I think there I was barking up the wrong tree, and might have thought of thrombosis or embolism from the start as a more important factor. I would like to ask Professor Harrison why he thinks there was a thrombus in the right atrium, and if he would agree that thrombi in the right atrium are extremely uncommon in the absence of obstruction to the tricuspid valve, previous pulmonary hypertension, or some obstructive lesion within the right atrium such as a tumour?

Professor HARRISON: It was ventricle.

Dr. GOODWIN: Ventricle, I'm sorry. I think the same points still apply, however, and it must be distinctly unusual in the absence of a previous infarct, some obstructive lesion, or previous right ventricular hypertension. Does Professor Harrison really think that the obliteration of the pulmonary vascular bed was entirely due to emboli?

The ischaemic fibrosis in the myocardium looks to me very like the sort of thing one sees in people with severe pulmonary stenosis or severe aortic stenosis, and we recall that the patient did in fact have angina, so I would think that Professor Harrison's suggestion that this fibrosis was due to poor coronary filling, resulting from a low cardiac output, which in turn was due to the pulmonary hypertension, was a very good one. Finally, the question of treatment. I think one is becoming more and more convinced that obliterative pulmonary hypertension is very often due to microscopic thrombosis or embolism, and, even if this is not the case, *secondary* thrombosis is very liable to occur. I think if I had realized this in 1955 or 1956 I would have, at almost any risk, put this patient on long-term anticoagulants, despite her haematological disorder and various other relative contraindications. In a patient with obliterative pulmonary hypertension, long-term anticoagulant therapy really offers the best chance of prolonging life. I don't think for a moment that it is always completely effective, but it often does help and it might well have helped this patient.

ACQUIRED HAEMOLYTIC ANAEMIA AND POLYARTHRITIS

Professor DACIE: I find it difficult to make constructive comments, because we don't know the cause of acquired haemolytic anaemia. However, most people nowadays refer to it as an auto-immune disease. Two hypotheses are currently favoured: One is that a race of antibody-forming cells develops in the body for unknown reasons, possibly as the result of somatic mutation, and that these cells continuously form proteins which act as auto-antibodies and destroy the patient's own cells. The second hypothesis is that an abnormal or denatured protein, adsorbed on to red cells, acts as antigen and that the antigen stimulates the antibody-forming cells to form antibodies which secondarily act on the patient's cells. This sort of hypothesis could, I suppose, be linked with theories of the genesis of rheumatic disease. The points in favour of a collagen-disease type of origin for this patient's disorder were, I think, the acquired haemolytic anaemia, the fact that she did develop overt rheumatoid arthritis, the biologically false-positive Wassermann and Kahn reactions —I don't think that there was positive evidence of syphilis —and the abnormal protein pattern in her serum that

she had from the start of her illness. I wonder whether Dr. Dixon would like to carry on from here and comment on her rheumatoid disease and the acquired haemolytic anaemia ?

Professor MCMICHAEL: The part played by the rheumatoid arthritis ought to be discussed.

Dr. ST. J. DIXON: Dr. Goodwin first called this an "auto-immune" disease, and there has in fact been demonstrated a circulating auto-antibody in this case. This is rather a rare thing in many of these so-called auto-immune diseases. As regards the arthritis, I don't think I can add any more to what Professor Dacie has said earlier in connexion with idiopathic thrombocytopenic purpura—namely, that cases of acquired haemolytic anaemia are quite frequently associated with a transient polyarthritis and rather more rarely with a chronic polyarthritis. Whether this patient had acute *rheumatoid* arthritis I don't know, because we have no further diagnostic evidence.

FALSE-POSITIVE W.R.

I should like to make a point about the "biological-false-positive" Wassermann reaction. I don't know whether you are correct in assuming that this could not be syphilis. We don't really know enough about the long-term behaviour of the "biological-false-positive" reactions. Here was a patient whose auto-immune disease, if we can use that word, got worse and worse and yet her "biological-false-positive" test became negative after antisyphilitic treatment. Do "biological-false-positive" tests become negative when the disease continues ? Dr. Scott, I think you have made some observations on this. Can you answer that question ?

Dr. J. T. SCOTT: Usually the biological-false-positive test remains positive, and the fact that it reversed to negative after treatment would be very strong presumptive evidence that it was syphilitic.

Professor MCMICHAEL: We have had no evidence in the necropsy that there was anything of syphilitic character here. False-positive, or anti-complementary, Wassermann reactions are well recognized in haemolytic anaemia.

Professor DACIE: I think that there was plenty of evidence of disturbed protein formation. Of course Dr. Dixon may be right that the patient had syphilis. I am not sure how we can prove it. I believe that a treponemal immobilization test was carried out. If so, would you agree that if that was negative, as I think it was, it would rule out syphilis ?

Dr. DIXON: That would almost certainly rule it out, but why did these tests become negative, which they certainly did, over a course of years ?

Professor DACIE: From the acquired haemolytic anaemia point of view the spleen was very big, and this was an interesting and unusual feature. The histology, I think Professor Harrison would agree, was rather like that described in "hypersplenism" of unknown origin. This is unusual in acquired haemolytic anaemia and my impression is that we are witnessing a conglomeration of very unusual pathological findings.

Professor HARRISON: Yes.

Dr. GOODWIN: There are some complicated tests from the V.D. Reference Laboratory: treponemal Wassermann reaction negative; standard Wassermann reaction negative; Price's precipitation reaction also negative (in 1958). We did repeated Wassermann reactions, as you will see later, and I am sure that a treponemal immobilization test *was* done, but I can't remember the result.

PULMONARY MICRO-EMBOLI

Dr. B. E. HEARD: Infarcts of the lung are commoner in the lower lobes than the upper, and, experimentally, medium-sized emboli can be found more often in the lower lobes than the upper lobes (Pryce and Heard, 1956). Did you, Professor Harrison, find more vascular change secondary to emboli in the lower lobes than in the upper? Dr. Goodwin pointed to changes in the upper part of the chest in the *x*-ray in life, and you pointed to the lower part of your post-mortem *x*-ray of the injected pulmonary arteries.

Professor HARRISON: The reason for my pointing to the lower lobe was that it was the one bit that I could reach. Secondly, it is one of the bits of the lung where the tissue is thin enough to give you good contrast when you take an *x*-ray picture. So it's a good place to look at and I could reach it. In fact these micro-embolic lesions are pretty evenly and widely distributed. I think I am right in saying that the reason why ordinary pulmonary emboli, the ordinary things you can see in an animal, go to the lower lobes dominantly is that they follow the axial stream. The blood sweeps round on two curves and the large chunks of tissue floating around go with the axial stream and land up along that line. But these things are *micro*-emboli; we didn't see any that were big enough to be visible with the naked eye. I went over these slides even with a hand lens and completely failed to find vascular disease. It wasn't until I had the microscope on them that I could find them.

Dr. HEARD: Of course miliary tuberculosis is evenly distributed through the lungs, and those are *micro*-emboli. But just how small were these emboli ?

Professor HARRISON: Oh, less than 1 millimetre.

Dr. HEARD: Could they be in some way related to the haemolytic anaemia ? Sickle-cell anaemia gives rise to pulmonary hypertension in this way on occasion. Is that stretching things a bit too far ?

Professor DACIE: The haemolytic anaemia was very much better at the time the pulmonary lesions were developing. I don't think there is any reason to suppose that auto-agglutination occurred at body temperature, although you could conceive that this could cause micro-embolization. I wonder whether splenectomy was in any way responsible ? Do you think the thrombosis in the ventricle could conceivably result from changes in the blood after splenectomy ? I may say that her platelet count was never very high.

Professor MCMICHAEL: It rose to 280,000 after splenectomy. Is that high ?

Professor DACIE: No, Sir, I would call that normal.

Professor MCMICHAEL: I remember Dr. Bedson saying that the tendency to thrombosis would not be influenced by the number of platelets, any more than the tendency to an explosion would be determined by one pound or two tons of dynamite.

Dr. C. C. BOOTH: May I inquire about one thing, Sir ? Can anybody tell us whether you ever get thrombotic thrombocytopenic purpura producing this sort of picture, and whether there is any relationship between that and haemolytic anaemia ?

Professor HARRISON: Are you referring to the Moschcowitz syndrome? I can only say there was no microscopical evidence for it in the kidneys or other small arterioles.

Dr. BOOTH: But what would be the microscopical evidence?

Professor HARRISON: We would expect in the kidneys these tiny capillary-sized lesions. It used to be thought that they were agglutinations of platelets blocking the vessels. It is known to-day as a primary vascular disorder and that these are probably local thrombotic lesions. But whatever their nature, I think I can safely say that we didn't find any.

Conclusion

Professor MCMICHAEL: Are we to accept that this patient had four separate disorders? She had (1) a haemolytic anaemia which was relieved by splenectomy; (2) a phase of acute rheumatoid arthritis which burnt out; (3) an aortic valve lesion which may possibly be related to the rheumatoid arthritis; and (4) this curious thrombosing condition in her right ventricle which led on to pulmonary hypertension. Is there no connexion or link between them at all? We did try to put them together by thoughts of "collagen disease."

Professor HARRISON: I think I should make one negative point. Collagen disease has been spoken of so often, let me say we did *not* find anything to suggest the Libman-Sachs endocarditis.

Dr. DIXON: Were the joints examined *post mortem*, Professor Harrison?

Professor HARRISON: Neither the joints, nor brain. We were a little inhibited in this case.

Dr. GOODWIN: Clinically her joints settled fairly rapidly and within a period of a few months they had cleared up completely, there being no *residua* at all.

Professor MCMICHAEL: Has anybody in the audience ever seen this combination of circumstances before, or is the case unique? No volunteers! We conclude that this patient had several disorders the connexion between which is obscure.

We are grateful to Dr. J. P. Shillingford and Dr. B. E. Heard for assistance in preparing this report, and to the photographic department of the Postgraduate Medical School for the illustrations. Charts 1 and 2 are reproduced, with permission, from Dacie, J. V., *Haemolytic Anaemias: Congenital and Acquired* (1954): Churchill, London.

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In a report on aspects of health in New Zealand, the Director-General of Health, Dr. H. B. Turbott, says the Maori people still have a long way to go before they are as healthy as their European compatriots. Of particular note, he writes, is the high rate of deaths among Maoris from road accidents, and their higher susceptibility to tuberculosis, cancer, and infectious diseases. (New Zealand, A22/60.)

SUPERSONIC AND HYPERSONIC FLIGHT

FIFTH EUROPEAN CONGRESS OF AVIATION MEDICINE

[FROM A SPECIAL CORRESPONDENT]

The fifth European Congress of Aviation Medicine was held in London from August 29 to September 2, delegates coming from 30 countries. The congress organization council, consisting of eight leading aviation medical men under the chairmanship of Dr. A. BUCHANAN BARBOUR (British European Airways), kept them fully occupied. After the opening by the Minister of Aviation, there was a very full scientific programme at the Royal College of Surgeons of England, as well as numerous social events.

The overall theme of the congress was "Human Problems of Supersonic and Hypersonic Flight." Although pedants may quibble over the prefixes, these terms are used to define flight at true airspeeds of respectively one to five, and more than five, times the speed of sound. The scientific programme was subdivided into six sessions. Concurrently there was an exhibition by firms manufacturing various materia aeromedica and equipment concerned with hygiene, comfort, safety, and survival in aviation. One day was devoted to a visit to the Royal Air Force Institution of Aviation Medicine at Farnborough, where delegates saw a thorough presentation, through displays, films, and demonstration, of the physiological and psychological research conducted there.

Aircrew Selection

One of the trends in aviation medicine which received special emphasis during the congress was the influence of the changing role of the human operator in modern high-performance flight upon the criteria of selection of aircrew and the maintenance of their efficiency. In his opening paper of the first session, Sir FREDERIC BARTLETT, F.R.S., reviewed the development of selection techniques for aircrew from about 1910, when the use of special tests for specific abilities began, through the period of the second world war, when importance was attached to instrument-reading and adaptability to technical aids in flying, up to the present era, when a new phase is dawning. Future flying personnel would require less specialized and more general abilities—alertness, quickness of decision, endurance, and adaptability to unusual conditions—abilities which would be difficult to define and to detect and measure in aircrew candidates. Within limits, Sir Frederic suggested, medical standards of fitness could be revised and perhaps eased. With automatic flight-control systems to some extent relegating the pilot to a mainly supervisory role, vision and hearing, for example, might perhaps be less important in future aircrew. The first essential in any candidate would rather be reliability, dependent upon a well-balanced nervous system capable of remaining efficient under unusual environmental stresses.

Air Vice-Marshal Sir AUBREY RUMBALL reviewed the problems of coronary artery disease and the early detection of latent myocardial ischaemia in the light of extensive surveys of Royal Air Force personnel. He incidentally suggested a need for caution in considering coronary artery disease as a risk in airline pilots—a risk possibly given undue importance in some quarters by conclusions drawn from necropsies on aircrew involved in fatal accidents. A number of subsidiary papers revealed the continuing Continental enthusiasm for intricate medical selection procedures.

Supersonic Airliners

Hitherto, aviation medicine has been essentially a military science, but it was clear from many of the papers read at the congress that developments in civil aviation in the immediate future will create their own physiological and psychological problems. This is especially true of the proposed supersonic airliner, which involves a large jump in speed, as well as radical changes in aircraft design and in the flight environment. In discussing this aircraft, Mr. C. S. R. MARSHALL (chief systems engineer, Advanced Project Group, Hawker Siddeley Aviation) stressed the changing role of the human pilot. The pilot would become a link in a semi-automatic flight-control system and his primary task would be to monitor and diagnose faults in the system in the air. In the design of future flight-control systems the aeronautical engineer would be increasingly dependent upon physiological data, particularly upon the "operating characteristics" of man. Further research was also needed on the reactions of passengers to the peculiar environmental conditions of long-distance supersonic flight. In the following address, on the requirements for biological research in relation to supersonic flight, Air Commodore W. K. STEWART pointed out that relatively little was known about the reactions to flying of ordinary passengers (as opposed to selected aircrew in special conditions). The group psychology of passengers might be very important in unusual conditions of flight. The prospect of supersonic airliners with windowless passenger cabins was mentioned, as well as the possibility of other potentially stressful features, such as accelerations of kinds not hitherto imposed on passengers in commercial aviation.

The subsidiary papers in this session included a number of communications on environmental and sensory physiology, with particular reference to the reduction of aircrew performance by environmental stresses, including disorientation due to angular accelerations. Surgeon Lieutenant I. H. COLLEY described the influence of age and of excess body weight upon dysbarism,* and Drs. L. TABUSSE and J. P. MARTINEAU (France) discussed the endocrinological factors in the reactions of aircrew to flying stress.

Aircrew Performance

Opening a session devoted largely to applied psychology, Captain A. M. A. MAJENDIE (director of operational research, Smith's Aircraft Instruments Ltd.) further discussed the relationship between human aircrew and automatic systems in high-performance aircraft. He was particularly concerned with the rapid conveyance of flight information to the human operator and described current attempts to solve this intricate problem. A sharp difference of opinion about the value of presenting information via the peripheral visual field was evident from a subsidiary paper by Mr. V. D. HOPKIN (R.A.F. Institute of Aviation Medicine). Group Captain H. P. RUFFELL SMITH (specialist in aviation physiology, R.A.F.) spoke on the need for recording aircrew performance-data in flight and mentioned the human difficulty of overcoming the innate suspicion in which aviation medical field research was sometimes held by aircrew and operators. He thought that it might prove desirable for data-recorders to be carried in all future transport aircraft so that aircrew performance could be measured in flight, to be correlated with such factors as the work-load or certain characteristics of the pilot, including age. Experiments in the recording of physiological data in transport aircraft were described in somewhat general terms by N. SERGEEV and A. I. VOROBIEV (Institute of Civil Aviation, Moscow, U.S.S.R.) in a paper submitted later in the congress.

Flight Environment and Safety

In an entertaining discourse on the prospect of supersonic airline travel, Mr. PETER MASEFIELD, former president of the Royal Aeronautical Society, declared himself strongly against the policy of building windowless passenger aircraft. It would be, he thought, "commercial suicide." For various logistic reasons, he also favoured an operating speed for the long-haul airliner of around three times rather than only twice the speed of sound. A speed of Mach 3 implies an all-steel aircraft and raises many new problems in environmental physiology concerning the crew and passengers. Some of these problems—for example, cabin pressurization and conditioning and protection against heat, noise, and vibration—were reviewed by Dr. D. McK. KERSLAKE (R.A.F. Institute of Aviation Medicine) with reference to both civil and military supersonic flight. He pointed out that there must be some compromise between the provision of the "ideal" physiological environment and the achievement of maximal operating efficiency of the aircraft. The subsidiary papers in this session described specific pieces of physiological research generally related to the requirements for protection against severe environmental conditions (acceleration, vibration, decompression, and heat) in high-performance flight. Major C. A. BERRY (United States Air Force), in a succinct review of the incidence, aetiology, and management of dysbarism in U.S.A.F. practice, described a case of dysbarism resulting in the medical retirement with persisting disability of an Air Force pilot, and reminded us that, despite technological progress, dysbarism was still a serious hazard of aviation, even at comparatively modest altitudes.

Efficiency and Ground-control Systems

The opening papers of this session—by Mr. W. C. WOODRUFF (chief controller, London Airport) and Dr. E. C. POULTON (Medical Research Council), who described research on vigilance—emphasized the importance of studying human performance in control in situations outside the aircraft. The limitations of man in monitoring complex displays and making rapid and vital decisions must be considered in the design of ground-control systems. Of the subsidiary papers, those concerned particularly with the health of ground personnel included a commentary by Drs. A. ROBERT and A. LUCAS (Air France) on the need for thorough and repeated audiometric studies of ground staff exposed to noise from jet aircraft, and a report by Dr. S. HADUCH and his colleagues (Military Institute of Aviation Medicine, Poland) on harmful effects of ultra-high-frequency radio waves. The latter workers had followed up cases of long-term exposure (up to 9 years) at "relatively high" energy densities. Apart from signs of "vegetative neurosis" resulting from prolonged exposure, the most notable effects of irradiation they described were neutropenia accompanied by monocytosis and, sometimes, eosinophilia. Present in over 50% of cases, these blood changes could not be correlated with exposure but were considered by the authors to be a sensitive index of individual susceptibility.

Miscellaneous Papers

The final session contained a miscellany of short communications on clinical and physiological topics. Group Captain A. H. MARSH (Director of Medical Services (Air), Royal New Zealand Air Force) described the interesting case of an experienced airline captain who also had had to be grounded owing to a deteriorating exophoria with an associated chronic tension syndrome, it later transpiring that an identical twin, flying as a captain in another airline, had also had to be permanently grounded with a florid tension syndrome. Group Captain Marsh stressed the fact that neither airline company employed a medical officer and suggested that, in the first case at least, adequate medical supervision might possibly have forestalled, or at any rate postponed, the premature grounding of an experienced pilot.

In view of a previous report that military jet flyers were prone to lesions of the cervical spine, Dr. R. J. HAMBURGER (Netherlands) and his colleagues presented a survey of 300

*Maladies due to variations in barometric pressure.

pilots and candidates, radiographs of whose cervical spines had been examined for arthrotic changes and changes in mobility. No significant difference in the incidence of arthrotic changes had been found between the pilots and the group of candidates with no flying hours to their credit. A greater mobility of the candidate-pilots' cervical spines (especially on retroflexion) was attributable to their being on average some years younger. The authors therefore concluded that abnormalities of the cervical spine found in former jet flyers were the result of ageing rather than aviation.

Nova et Vetera

RABELAIS AND LETTUCES

The fact that in my youth I wrote an unsuccessful essay upon "Medical Aspects of the Life of François Rabelais" in a Medical College competition, at first—and even at second—sight might suggest little connexion with my view that lettuces are not what they were. For a long time I have believed that this fundamental constituent of a good salad has been ruined by mass-production methods—forcing under glass upon artificially fertilized composts. Of course those who know me would readily have said that my opinion was based upon a taste vitiated by pipe tobacco. On the other hand, I have felt justified in it by the readiness with which so many people enliven their tasteless salads with mayonnaise and other salad creams. What has this to do with Rabelais, whose writings upon Gargantua and Pantagruel would suggest that in mediaeval feasting there was a grossness that allowed for little in the way of refinement?

Recently I was the guest of a French medical society in Lyons, which city, among many other great qualities, is proud of its reputation as "la capitale de la gastronomie française." The chief day was a Friday and for lunch we were taken to the great mediaeval hospital, the Hôtel Dieu. An excellent convent meal was set before us, the third course of which was "les filets d'ombles et la salade mimosa." Momentarily my mind was removed from the salad by the poetry of *les ombles*, fish that are found only in the depth of the blue pools of the high French Alps. But the salad: essentially a simple lettuce, but a lettuce the like of which I have not tasted in England for 40 years. As a medical student on a Saturday afternoon I used to walk across Richmond Park to Sheen, where it was possible to get a high tea enlivened by a most delectable lettuce. On that Friday at Lyons my memory was taken back to those salad days at Richmond and it was also stimulated by being told by my companions at lunch that I was sitting near the place where François Rabelais must often have had his meals when, in about 1533, he was a physician at the Hôtel Dieu. They say that one's most vivid memories are based upon the sense of smell, and it may well be that my association tracts, reinforced by the memory of the circumstances of my student days, contributed to my appreciation of the lettuce of Lyons. Nevertheless, on my return to England I was very strongly of the opinion that English lettuces at any rate are not what they were.

As to Rabelais himself, we should remember that apart from the mediaeval coarseness which is so foreign to our present literary taste, his allegorical stories had a great deal of power in counteracting the evil influences of the monastic system of his time. As to his medical work, little is known of it except that he produced an edition of the aphorisms of Hippocrates and of the *Ars Parva* of Galen, together with an edition of the medical epistles of Manardus, who followed Galen. I also like to think of Rabelais as one of the pioneers of French liberalism. His idea of co-education as portrayed in the story of the Abbey of Thelema was certainly three hundred years or more in advance of his time.

NORMAN CAPENER.

To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in current use.

Paromomycin

"Humatin" (Parke, Davis).

Composition.—Paromomycin, or humycin, is an antibiotic prepared from culture-filtrates of a strain of *Streptomyces* (P-D 04998), resembling *S. rimosus* (NRRL 2234), isolated from soil collected in Colombia. Chemically it is a glycoside of D-glucosamine. Humatin is a stable, white, amorphous, water-soluble substance, consisting of the sulphate of the antibiotic. It is put up in capsules each containing the equivalent of 250 mg. of the antibiotic base.

In-vitro Activity.—Paromomycin, is active against both Gram-negative and Gram-positive and against acid-fast bacteria, including the human tubercle bacillus, and it is effective against *Shigella* and *Salmonella* spp. It also is active *in vitro* against many fungi, including *Actinomyces bovis*. It is ineffective against various strains of virus *in vitro*, even in the highest concentration which leaves undamaged the supporting cell cultures. It is directly amoebicidal to cultures of *Entamoeba histolytica*, the protozoan parasite which causes amoebic dysentery. This latter feature is of particular significance because no antibiotic so far has been found to be directly amoebicidal, non-toxic, and therapeutically effective in adequate degree in men suffering from amoebiasis.

Pharmacology.—When given parenterally in low doses to laboratory animals paromomycin is highly effective against many bacterial infections, including *Shigella flexneri* and *Sh. sonnei*. It is less so against tubercle and *Salmonella typhi-murium* in mice. The drug is poorly absorbed from the bowel; therefore when given orally it is relatively ineffective against systemic infections.

The observation that paromomycin is directly amoebicidal to cultures of *E. histolytica*, an organism which primarily is localized in the large intestine, suggests that its poor absorption from the bowel may be an advantage in the therapy of this infection. Oral treatment of rats and of dogs having intestinal infections with this protozoon proved very effective irrespective of the degree of pathogenicity. Parenteral treatment of amoebic liver infections in hamsters caused some restriction of the infection.

Therapy.—The drug is available only in capsules for oral treatment; it is therefore intended solely for infections localized within the bowel, whether bacterial or protozoan. At a dosage of 80 mg./kg. body weight it has been used successfully and safely for the eradication of *Shigella sonnei* and enteropathogenic *Escherichia coli* infections in children, both in patients suffering from enteritis and carriers of the infections. It has also been reported as effective in the clearance of *Salmonella* infections of the food-poisoning type, and of other forms of bacterial enteritis.

Reports are becoming available on the treatment of intestinal amoebiasis. The doses ranged from 4 mg./kg. to 50 mg./kg. daily, usually continued over five days but in some cases for longer or shorter periods. In general a dose of more than 12.5 mg./kg. daily, sustained for five days, has been found almost invariably to be rapidly effective in controlling the infection and in eradicating it from the intestine. When inadequate dosage fails to cure the infection, subsequent re-treatment in adequate dosage is likely to be effective, without any suggestion of the development of antibiotic resistance. There appear to be no contraindications to the administration of paromomycin by mouth to patients of any age for this purpose.

Side-effects.—If given parenterally in high or prolonged dosage paromomycin may cause renal damage; this is arrested and repaired on stopping the drug. Given orally the drug is relatively non-toxic, but it may cause some diarrhoea, which is roughly proportional to the dosage.

N.H.S. Basic Price.—250-mg. capsules, 16 for 40s.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Our Hospitals

SIR,—We must be grateful to the *British Medical Journal* for the Special Hospital Number (September 10), as the subjects discussed have now become so realistic. Hitherto many of us have talked and worked for years on new hospital proposals. Now it seems as if we might build and replace some of our worn-out institutions. As an architectural problem a hospital is probably the most complex of all structures, and not only are the functions multiple but architect and medical authority must face a rapidly changing future, and metaphorically risk the fate of false prophets. Before designing a general hospital there are three main considerations: (1) a sociological survey of the community's needs, both quantitative and qualitative; (2) the expected development in medical and nursing methods and relationships; (3) the provision for graduate and postgraduate education, not only of doctors but of nurses and medical ancillary staff. Important as these studies are, there is an immediate necessity to replace worn-out and inadequate hospitals, and the problem here can be so obvious in its dimensions that we need not wait for all the answers, answers which in most cases are tentative and only indicate trends.

I regret that amongst your contributors there were only two clinicians. Lord Taylor's note (p. 752) seems to be addressed mainly to those responsible for over-all planning—namely, the Ministry of Health and the regional boards—and I am sure they will be grateful for his advice. They have now had 12 years to consolidate the working of the N.H.S. Act and are in a position to plan ahead. I have great admiration for their work, but at this juncture I fear that the clinician and the nurse, whose intimate work with patients is the *raison d'être* of a hospital, are inadequately considered on the excuse that they cannot express or control their individual requirements, that they cannot work as a team in hospital design, or compromise in the use of common units. But in the planning the regional boards must have the courage of their convictions. If, for example, a plan to replace three small hospitals by one larger hospital is the logical result of their investigations, then if public clamour is to be avoided the first principle of rationalization must be conceded—that is, no injustice must be done to permanent staff. Objections on the grounds of sentiment and tradition are fed by lack of good publicity, as well as by staff fears of dismissal or degrading.

Evidence from Social Surveys

Repeated reference to certain social surveys deserves special comment, as they are quoted without criticism. That of Forsyth and Logan[1] and previous surveys do not really show what beds are required, but only that existing bed provision is a guide, provided that addition is made to deal with waiting-lists. The evidence that there is no other unfulfilled demand is vitiated by the acceptance of existing turnover rates, and by imponderables such as patients' unwillingness to go into such hospitals as they describe. The real importance of this report is the description of the primitive and inadequate conditions suffered by patients, doctors, and nurses in a particular hospital group. This is literally shocking reading. But there are other weaknesses in this report, such as the suggestion that the general practitioner is to blame for lack of integration with hospital service in order to increase an already high turnover rate. Why should we increase the turnover rate to approach the U.S.A. figures when the latter are determined by entirely different social and economic conditions? Human beings do not want to be pushed through a sausage machine. But why blame the G.P.? It is the G.P. himself who demands closer liaison with the hospitals. Here I would like to suggest that hospital almoner departments should be organized by the local health authority so that social workers, health visitor, and district nurse can be available together in the hospital unit so that G.P. and consultant can deal with patient problems in a more continuous way. This would help to train both groups of doctors to deal with social conditions and to use appropriate agencies, and enable the consultant to see the G.P.'s problem, and teachers to learn the importance of social medicine in all its implications to which at present they hardly give lip-service. Forsyth and Logan, following Crombie and Cross,[2] make much ado about the number of in-patients who do not "need" specific hospital service, but who have been admitted to, or kept in, hospital for social reasons. If a febrile or disabled patient cannot get his meals, or have his bed made, or himself washed, or his excretory functions attended to at home, why not look after him in hospital?—that is precisely one of the functions of a hospital.

I will not make any comments on nursing problems, as my examination of some first principles will be published elsewhere, except to register my opinion that the leaders of the nursing profession are leading us rapidly in the way of U.S.A. difficulties.

Hospital Design

As regards hospital design, I fear we are showing little forethought and no courage. Despite Dr. E. Rosenfeld's opinion expressed at a meeting at St. George's Hospital recently, we are not nearly ready for any standardization in design. We have to make a big leap forward from our existing but already out-of-date ideas. The idea of the open ward, a dormitory, or doss-house for the sick is still with us, though we know it must be broken down into small units for the sake of privacy, quiet, and safety from cross-infection. Many of us resist this breakdown because of long usage and insensitivity to the horror of the open ward, and we invent excuses against planning small units, such as poor observation, the disinclination of our docile patients to demand privacy (except for remunerative private wards), difficulties in teaching, etc., all of which are utterly false, and misleading to architects, who have enough difficulties with their expensive perimeters, plumbing, ventilation, light and heating services not to welcome easier specifications. But at what point of subdivision should the breakdown of the ward into small units stop? For there is no good reason left (except cost) to let us be satisfied to leave our privacy at home, to be forced into group-living and group-sleeping when we are sick. Everywhere in advanced countries, except Britain, wards are accepted at the breakdown level of four- to six-bed units with a number of single rooms; the Nuffield projects are well behind the times with larger units divided into open bays with relatively few single rooms. This latter group will be used for noisy patients, for dying patients (a clumsy way of informing such patients), for V.I.P.s, and for isolation of infected cases (i.e., "locking the stable door . . ."). There is only one logical point to stop at in this breakdown and that is the provision of single bedrooms only—anything else is a compromise based on economy and architectural difficulty. Mr. R. Vaughan Hudson[3] has proposed that we convert every possible open ward into single rooms, argues the case refreshingly, but unfortunately impracticably, so that no discussion has been aroused. A ward of single bedrooms can be designed with its busy end where intensive nursing care can be located, and patients moved away from this station as their needs diminish. Observation (using partial glass partitions) and communication system would be improved compared with the bush telegraph system of the open ward, sanitation can be provided for washing and management of excretory functions so as to reduce nurses' work, ventilation can suit

the individual. Treatment room and sluice room become unnecessary—but day rooms must be provided. Patients' histories can be taken in privacy, complete flexibility as regards male and female admissions is possible, noise reduction is maximal, and visiting hours are not a penance for the very ill patient. I could continue this list of advantages. Yet Professor R. Llewelyn Davies (p. 768) thinks that the "race track" ward is not suitable here, nor the problem of central supply to be so important a determinant in hospital design. But surely he must realize that what he calls "revolutionary methods of supply and storage" are inevitable and will save nurses work far more than herding patients together at 7-foot centres. I suggest he tries to move a bed out of a six-bed cluster or help to move a patient on to the unnecessary trolley required in close-bed groups. I refuse to be dazzled by the Nuffield experimental wards; hospitals built in Basle, Stockholm, U.S.A. nearly two decades ago have shown the way—see, for example, Rosenfeld and Abramson.[4]

Costs and Planning

Lord Taylor may be right when he tells us to prepare a complete specification before briefing the architect, but this method is inhibiting at a time when new ideas are badly wanted. Architects must work to a module logically related to the sort of areas and cubes specified and their help is needed at an early stage in a country where few clinicians have had experience in hospital design. But Lord Taylor's suggestion that money comes first and that we must build to fixed unexpandable sums will enormously increase the risk that incomplete hospitals will be built and the last phases left on paper. I would rather see fewer but complete hospitals erected than have hospitals consist of a mixture of new building and old slums. This is the problem for the Ministry. Economy is difficult to define, but money spent on permanent or semi-permanent finishes, easy cleaning and maintenance method can help to keep maintenance labour and charges down. Abel and Lewin[5] were probably correct in their estimate of hospital reconstruction expenditure—a sufficient sum would make it easier to promote complete schemes.

Dr. J. D. Spillane (p. 778) is to be congratulated on a most discriminating and helpful report. He has not been bemused by "solemn nonsense" but does portray the liveliness of approach in the American medical schools that we do not show here. I would recommend that his paragraph on Departments of Behavioural Science should be reprinted in large type and a framed copy be fastened to the desk of every medical school dean until such day as its message has been perceived. The unit in medicine is the whole person, and the study of the whole person in his culture will give us the answers to the question of general practitioner and consultant spheres of action, the integrated care of the patient till he has achieved maximum recovery, the provision of rehabilitation and geriatric service, and the care of a human being as a psychosomatic unit. Professor T. McKeown's community hospital[6 7] is the right mechanical background for our work.—I am, etc.,

London, W.1. HUGH GAINSBOROUGH.

REFERENCES

1 Forsyth, G., and Logan, R. F. L., *The Demand for Medical Care*, 1960. Oxford Univ. Press, London.
2 Crombie, D. L., and Cross, K. W., *Med. Press*, 1959, **242**, 316, 340.
3 Hudson, R. V., *Lancet*, 1960, **2**, 90.
4 Rosenfeld, E. D., and Abramson, L. A., *Modern Hospital*, 1954, No. 5, pp. 67 and 70.
5 Abel, A. L., and Lewin, W., *Brit. med. J.*, 1959, **1**, *Suppl.*, p. 109.
6 McKeown, T., *Lancet*, 1958, **1**, 701.
7 —— *Brit. med. J.*, 1959, **1**, Suppl., p. 122.

SIR,—In your Special Hospital Number (September 10) some concern was shown at the apparently huge cost of building new hospitals. In what sense is a modern hospital expensive?

Capital expenditure provides those working in hospitals with new tools to assist them in their task of providing medical care. It partly represents completely new hospitals and equipment, and partly replacement. As with any other industry, the effectiveness and efficiency of those working in hospitals is to a considerable degree dependent upon the quantity of capital equipment supporting them. For instance, the high productivity of American industrial workers is largely due to the heavy investment of capital per worker.

Although the cost of building a modern general hospital seems large, it represents only a small fraction of its operating cost over its lifetime. At present a hospital which costs £6m. to build costs about £1m. annually to operate, and its expectation of life is roughly 100 years. This relatively low ratio of capital to recurrent costs indicates that the quantity of capital supporting each of those working in even a new hospital is low compared with most industries. Large numbers of British hospitals are now so old that their capital value should be regarded as fully depreciated. This implies that net capital investment per employee in many hospitals is zero. If the nation's prosperity continues to rise, labour will become increasingly expensive. It is thus essential that new hospitals should be designed and built so that labour requirements are kept to a minimum, thus allowing maximum time available for direct care of patients. This will certainly entail heavy capital expenditure when compared with the past. To accept this, however, is only to recognize that the days of plentiful, cheap labour, on which our hospital structure has been built, are gone for ever, and we must plan accordingly.—I am, etc.,

Richmond, Surrey. J. R. SEALE.

SIR,—When new hospitals are being planned, may I put in a plea for reception wards adjoining the casualty department, where cases admitted during the night can be treated and cared for until next morning? Those who have experienced the disturbance created in a large ward by an admission during the night know only too well how upsetting, and even distressing, it can be to other patients—the tramp of feet as the admission is carried in, the hurrying to and fro of nurses to attend the case, the entry of relatives; in some cases, preparation for theatre or a blood transfusion; in others the delirium or stertorous breathing of the acutely ill—all these must be distressing beyond measure to a sensitive patient who is trying vainly to sleep.

If such admissions could be dealt with in a reception ward manned by trained nurses, all this disturbance could be avoided and the patients transferred to the appropriate lying-in wards the following morning.—I am, etc.,

Manchester 23. MURIEL M. EDWARDS.

SIR,—In connexion with your Special Hospital Number (September 10), we are anxious that you should be acquainted with the views of some Harlow doctors. This letter is signed by one Harlow partnership, but we feel sure that many of our colleagues think as we do. We appreciate that much good work is done in converted Nissen huts, nevertheless we feel that our new town should by now have had a hospital. At present

some building is in progress, but we shall have no hospital beds in Harlow for about two to three years. We can only presume that this delay has been caused by the unwieldy machinery of the Treasury, the Ministry of Health, and the Regional Hospital Board, as well as by overplanning.

Cost is usually used as an excuse when everything else fails. This town rightly prides itself on its group practice centres and its industrial health service, which have been made possible through the generosity of the Nuffield Trust. If this trust had been approached for help in building the hospital, it might well have assisted both with the finance and the planning. This would have completed the "Harlow Experiment." At this late stage we can only hope that everyone concerned will proceed without further delay.—We are, etc.,

H. E. BACH.
J. R. W. SINTON.
MILDRED F. GORDON.
M. L. MARINKER.

Harlow, Essex.

"Celbenin"-resistant Staphylococci

SIR,—The discovery of a "penicillin" which is not inactivated by staphylococcal penicillinase is a major advance in the field of chemotherapy (September 3, p. 720). But it is perhaps a little early to take comfort from the idea that staphylococci cannot achieve resistance to it. In the early days of their discovery it was claimed for both chloramphenicol and chlortetracycline that bacterial resistance would not be a problem. In both cases the staphylococcus has had the last word. It may do so again.

It has been argued, on theoretical grounds, that the only form of penicillin-resistance shown by fully virulent staphylococci is that associated with the production of penicillinase. Thus it is suggested that virulent staphylococci will not become resistant to a "penicillin" which is unaffected by this enzyme. Leaving aside the possibility that staphylococci might produce a new or adapted enzyme (celbeninase ?), it should be pointed out that "celbenin" (BRL 1241) is by no means equivalent to penicillinase-resistant penicillin G. Penicillin-sensitive staphylococci, like all other penicillin-sensitive bacteria, are 20 to 50 times as resistant to celbenin as they are to penicillin G. This difference is of a magnitude which suggests to me that the mode of action of the two drugs might differ and that bacteria might develop different pathways of resistance to them.

In short experiments over a period of only a few months, I have passaged eight strains of *Staph. pyogenes* on celbenin ditch-plates. After 20 to 30 passages, two strains have yielded mutants resistant respectively to 50 and 100 μg./ml. Neither of the resistant mutants inactivates celbenin, although both, like their parent cultures, are penicillinase producers. Unlike staphylococci that have become tolerant to penicillin G *in vitro*, both the celbenin-resistant strains have remained typical cultures of *Staph. pyogenes* and have retained full coagulase activity. In prolonged laboratory studies with penicillin G I have never encountered similar resistant variants.

The proof of the pudding is, of course, in the eating, and it remains to be seen whether celbenin-resistant staphylococci occur *in vivo*. That they will not occur as frequently as do erythromycin- and novobiocin-resistant organisms is certain. Thus, if celbenin is reserved for penicillin-resistant infections and not used indiscriminately, it is unlikely that staphylococci resistant to it will be a serious problem. Fortunately the drug is both expensive and unsuitable for oral administration and is therefore likely to be used with discretion. Under these circumstances celbenin should prove an invaluable addition to our anti-staphylococcal armoury for many years to come.—I am, etc.,

MARY BARBER.

Postgraduate Medical School,
London W.12.

Gangrene from Thiopentone

SIR,—We have only recently had the opportunity to study the paper by Professor J. H. Burn (August 6, p. 414) entitled "Why Thiopentone Injected into an Artery May Cause Gangrene." He concludes that the gangrene is caused by vasoconstriction due to release of noradrenaline and quotes some of our work in support of this thesis.

Unfortunately Professor Burn appears to have misunderstood our article,[1] for he states that we performed sympathectomies and allowed time for the sympathetic fibres to degenerate before injecting thiopentone. In fact we performed the sympathectomies after the injections of thiopentone so that the sequence of events might more nearly resemble clinical conditions. The beneficial effects of sympathectomy cannot therefore be supposed to occur for the reason that he puts forward. The evidence from our experiments was that vasoconstriction did follow thiopentone injection into an artery, but it was of a transient nature lasting for thirty seconds or less and followed by a compensatory dilatation. Complete ischaemia of the part produced by clamping for fifteen minutes or more never produced necrosis, and so it cannot be presumed that ischaemia for half a minute could do so. The transient vasoconstriction which occurs after thiopentone injection into an artery may well be due to local release of noradrenaline, as Professor Burn suggests, but it is difficult to maintain that it can be the cause of the necrosis. We postulated that the beneficial effect of sympathectomy was probably due to hyperaemia and increased blood flow discouraging thrombosis in the vessel damaged by the thiopentone. That this might be so was further supported by experiments showing that heparinization had a beneficial effect.

Our recommendation as to the course to pursue in clinical practice was therefore ". . . where thiopentone has been injected into an artery during induction of anaesthesia it would seem best to avoid going on with the intended operation and to place the patient on intensive heparin therapy. Should postponement of the operation be dangerous, then neurectomy of the sympathetic supply to the affected limb should be performed surgically."—We are, etc.,

J. B. KINMONTH.
R. C. SHEPHERD.

Department of Surgery,
St. Thomas's Hospital Medical School,
London, S.E.1.

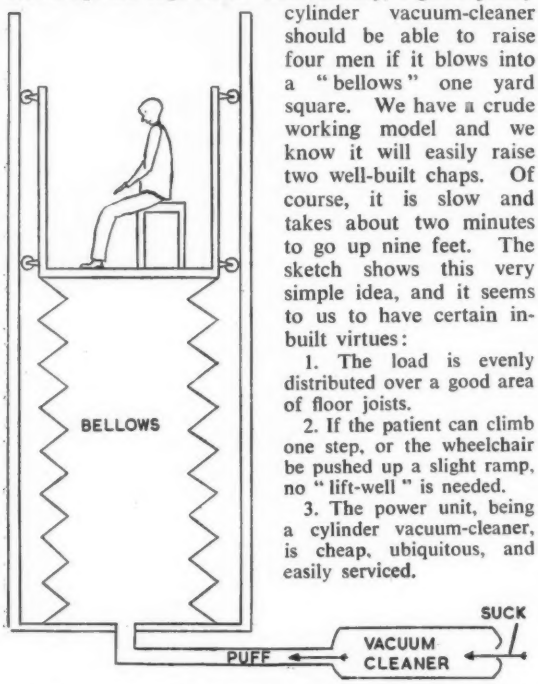
REFERENCE

[1] Kinmonth, J. B., and Shepherd, R. C., *Brit. med. J.*, 1959, **2**, 914.

Invalid Lift

SIR,—Working upon the principles which have been used for many years to raise aircraft of which the undercarriage has collapsed, and which have also been used to elevate paralysed patients from the bottom to the verge of their bathtubs, we have made a pneumatic lift which would elevate a patient from the ground to the first floor of his home.

Simply, our lift consists of a bellows similar to that of an old-fashioned camera, but very much bigger. On top of the bellows is a cage, and when the bellows is blown up, the cage rises. Theoretically, a good-quality cylinder vacuum-cleaner should be able to raise four men if it blows into a "bellows" one yard square. We have a crude working model and we know it will easily raise two well-built chaps. Of course, it is slow and takes about two minutes to go up nine feet. The sketch shows this very simple idea, and it seems to us to have certain in-built virtues:



1. The load is evenly distributed over a good area of floor joists.

2. If the patient can climb one step, or the wheelchair be pushed up a slight ramp, no "lift-well" is needed.

3. The power unit, being a cylinder vacuum-cleaner, is cheap, ubiquitous, and easily serviced.

4. Because the "bellows" contains so much air, if the "electrics" fail in any way, or if even a six-inch rent appears in the "bellows," the cage just saunters slowly down at about a foot a minute.

5. The scaffolding of the affair bears no serious weight. The carriage is pushed up by the bellows and the scaffolding simply guides it into a straight path. Thus the scaffolding can be made to measure from any of the commercialized "angles."

6. Because the "bellows" fill the space below the "cage," no one can get under it and one of the hazards of a conventional lift is eliminated.

We think that because the design is adaptable, and because the important components are already mass-produced, it might be possible to provide a "one-patient" lift in most homes for £150 to £200. It would depend, to some extent, upon whether the lift could be installed in a stair-well or whether one joist would have to be cut and braced in order to fit it into the corner of a room. Our working model raises us effectively, using a seven-year-old vacuum-cleaner, but it needs a good deal of refinement. Our colleagues in the Faculty of Engineering are willing to develop the idea properly if there is real evidence that a lift, at such a price, could contribute materially to the well-being of patients with severe respiratory, cardiac, or locomotor troubles. We think that such patients sometimes leave well-liked homes to move to bungalows and, in so doing, spend more money than this.

We would be very grateful if doctors who have views on this sort of thing would spare time to drop us a postcard so that we may conclude whether or not the idea is worth pursuing.—We are, etc.,

Department of Anaesthetics,
The Medical School,
Newcastle upon Tyne 1.

E. A. PASK.
N. BURN.

Fate of the Claudicator

SIR,—While reading the very interesting article on "The Fate of the Claudicator" by Mr. A. Singer and Professor Charles Rob, who present 109 cases of aorto-iliac thrombosis in the age group 38–77 (August 27, p. 633), I was reminded of an article dealing with the diagnosis and treatment of renal-artery stenosis by Professor W. S. Peart and his colleagues which you printed about a month previously (July 30, p. 327). Commenting on the incidence of renal-artery stenosis Professor Peart and his colleagues tell us "of 160 cases investigated in this way [renal arteriography, usually by the selective method], a renal artery lesion was demonstrated in 10. In eight of the other cases reported here [they report 22 cases altogether], renal artery narrowing was revealed at aortography *performed for other reasons (usually iliac or aortic stenosis . . .)*." [My italics.] This group included at least six "claudicators," all of whom were moderately hypertensive. This constitutes the precise group of cases which appear to have been dealt with in the article of Mr. Singer and Professor Rob, and I was keenly looking for a chance finding of a few cases of renal-artery stenosis in their series of 109 cases (which in no way is an insignificant number) during investigation of aorto-iliac thrombosis, and which incidentally included 51 cases of hypertension as well; however, I did not find any.

It is quite possible they have not mentioned this finding, if any, because it had not much relevance in the present context. But it would be very interesting to know whether they observed such findings, specially in view of the associated hypertension in about half the cases, a few amongst whom might have been candidates for Professor Peart and his colleagues' investigations and relevant therapy. Incidentally, the latter are on the staff of the same hospital as Mr. Singer and Professor Rob.—I am, etc.,

Edinburgh 3. SHYAMAL KUMAR SEN.

Operating on the Wrong Limb or Digit

SIR,—Nine instances of operations being performed on the wrong limb or digit in the course of one year is startling news indeed. Dr. P. H. Addison's suggestion (September 10, p. 806) that the digits should be named rather than numbered is one that ought certainly to be adopted in all hand surgery. However, a really foolproof method is needed in all branches of surgery.

A big cross made with Bonney's blue on the limb, and a smaller cross on the digit, are effective if it is one person's responsibility to make the marks. It should be done by the house-surgeon *or* the ward sister, but not both. We have found it useful also to make a mark on the side of a knee on which pain is felt, and down the leg which has sciatica before doing a laminectomy. When dealing with young children it is helpful to make the marks with the parents present on the evening before the operation.—I am, etc.,

St. George's Hospital,
London S.W.1. PETER R. FRENCH.

Sewage in the Sea

SIR,—In South Africa we also have sewage contamination of our coastal waters, and as an underwater diving naturalist I have been observing its effects over many years. In my opinion, the effect on the human being is not so important as the effect on the underwater life.

Physically, I observed, the sewage does not go into infinite dilution but remains as a body or "plume of smoke" underwater for a very long time, and its deposition is usually along the sublittoral zone up to two miles on either side of the sewage point of a 30,000-population group. If there is a storm, then surface drift may deposit pieces of sewage on a beach, but in ordinary weather it stays low down and sinks on to a 50- to 100-yard broad area just outside the low-water ebb line (sublittoral zone). It is common in such a zone to find rockfish with large sores on the side of the body. The reduction in number of rockfish when an area becomes affected is a very prominent feature. The sessile rock and sand population shows evidence of pathology up to two miles from a sewage point. By pathology I mean that sand and rock anemones have part of the body shrunken and necrobiotic while molluscs show a high incidence of hydroids invading their shells. Shells are covered, as are the underwater algae, by a lower-grade filamentous algal growth as well as incrustation by polyzoan and gypsinian colonies. So are the corals. This lime incrustation is only evident in such grand manifestation where the sewage slime is present. The water itself is easily clouded by the thin often mucous slime, which floats upwards when disturbed.

Because practically the whole of the pelagic and carnivorous sea life depends on the essential animalcule plant food-link along the shores, one can well imagine how essential it is to keep the shorelines over the world healthy from contamination of sea life. The direct effect on human beings and the indirect effect on them via the sea food has also not been investigated properly. It is not only a problem for England but it concerns the whole world, and I think should be taken up by a committee of a world body like United Nations.—I am, etc.,

Johannesburg. P. H. BOSHOFF.

SIR,—May I be permitted to reply to the impassioned appeal of Dr. K. J. Grant (September 3, p. 734) for the right to bathe in sewage-polluted sea water? As the mover of the "considerable alarm" addendum to which he refers, may I invite him to read the relevant part of the report of the proceedings of the Annual Representative Meeting (*Supplement*, June 25, p. 394), where he will note that I said: "No one would persuade the public that bathing in a mixture of sewage and sea water was other than objectionable, and (he) hoped that the report would not be used for the justification or authorization of continued fouling of bathing-beaches with untreated sewage."

Perhaps Dr. Grant will also re-read the "existing scientific evidence" in the report of the committee on bathing-beach contamination.[1] He will then notice admissions such as "Sea water samples as examined in the laboratory may therefore be considered more as washings of polluted material than as fair samples of total quantity of pollution to be assessed." "Lack of a suitable enrichment medium for dysentery bacilli precluded any further work on isolation of these organisms from sea water." "Because of the very large dilution factor, special concentration precedures would probably be required to isolate poliovirus from sea water." "Salmonella isolated from sea water increased with rising coliform counts."

One can derive no satisfactory evidence from the report that health risks due to viral infection from sea water are negligible. Nor do I believe that there would be no outcry if a public bathing-pool was found to have any coliform count at all, let alone 10,000 per 100 ml. of sea water which Dr. Grant is prepared to swallow. One must ask, "How revolting is revolting?" and also, "When does a beach cease to be *aesthetically very unsatisfactory—with negligible risk to health*, and become *so fouled as to become aesthetically revolting—with serious risk to health?*"

Dr. Grant has a perfect right, which I respect, to bathe in the emulsion of faecal products which sewage-contaminated sea water around our shores often is, but I will not, nor, I am convinced, should any other responsible practitioner, advise the public that such a procedure carries no risk to health.—I am, etc.,

Bradford. H. FIDLER.

REFERENCE

[1] *Sewage Contamination of Bathing Beaches in England and Wales*, Medical Research Council Memorandum No. 37, 1959. H.M.S.O., London.

SIR,—I fear that Dr. K. J. Grant (September 3, p. 734) has read into my letter (July 30, p. 385) more than it contained. Not for a moment would I dare to throw doubt on the findings of the Medical Research Council's report. I accept the contention that the risk of contracting infection by bathing on most British beaches is, statistically speaking and on the evidence available, very small. What I do not accept is the suggestion that the report makes it possible to be complacent about the whole business of seaside sewage disposal.

In spite of all Dr. Grant has to say, I stand by my contention that lack of evidence *may* be due to the difficulty of gathering it. The history of epidemiology from the earliest times is full of instances. In the present context, perhaps the greatest difficulty is that in most cases of infection following bathing there are several probable or possible source of infection, and only rarely does an organism bear a "trade-mark" which enables one to mark it down to one single source. In the outbreak to which I referred we had the great good fortune to be dealing with such an organism. The occurrence of even a single case of typhoid in someone whose only exposure to infection was during bathing—I apologize for not having specifically mentioned that he ate no cockles—is worthy of note.

That my illustration was drawn from an outbreak of typhoid was fortuitous and perhaps unfortunate, in that it provoked Dr. Grant into a not very relevant digression. How "enormous" in fact is the increase in the pollution of beaches and in sea-bathing? Is it not possible that the yearly number of cases of typhoid might have fallen still lower if there had been less pollution? I agree that the source of infection is "not infrequently" traced by the health departments, but there certainly remain apparently sporadic cases whose source of infection is not traced. Until someone proves that a patient has been infected from some specific source I consider it reasonable and even proper to consider all possible sources, even though some are less probable than others.

"The spread of typhoid by shellfish is not in question," says Dr. Grant. Who said it was? Certainly not I. The point at issue is whether typhoid bacilli or other organisms which are discharged into the sea in untreated sewage can cause illness in human beings. Whether they cause the illness by being swallowed direct or after being concentrated in shellfish or other foods, the fact remains that if they had not been discharged in the sewage the patient would not have ingested them. To imply that because infection of bathers is rare there is no harm in continuing to contaminate shellfish, which present a well-recognized hazard, is a curious kind of logic.

I fear that I am one of those ageing public health doctors who are conditioned to regard dirt as dangerous until it is proved innocent. For reasons for which, no doubt, some Freudian basis could be found, I have a particular prejudice against particles of infected faeces. I am commended when, in my daily work, I discourage food-handlers from spreading such particles on ham sandwiches, farm workers from stirring them into the

milk, and the water department's employees from depositing them in the municipal water supply, even though I know that the milk will later be pasteurized and the water chlorinated. I find it inconsistent to aid and abet the pouring of untreated faeces into the water people bathe in or the use of it for fattening delicacies for holidaymakers. Even the cautious M.R.C. report appeared to concede that on the "aesthetically revolting beaches" there might be danger to bathers which was not negligible. It might be a good beginning to name those beaches, though the vested interests of the seaside holiday industry would object. Great Yarmouth, Dr. Grant's town, has an important asset—the whole width of the North Sea into which to discharge its sewage. I am concerned about the less fortunate places which empty their excreta into land-locked bays or on to shores where a pattern of shoals has the effect of producing a semi-closed pool of sea. Surely they should receive the most meticulous consideration before they are given a clean bill of health, and if there is doubt caution is proper.—I am, etc.,

Public Health Department, Colchester. JOHN D. KERSHAW.

SIR,—Dr. K. J. Grant (September 3, p. 734) may be quite right, but personally I do not like bathing amongst faeces, anyhow.—I am, etc.,

Camberley, Surrey. J. C. HILL.

Deaths from Drowning

SIR,—Dr. F. W. Woodruff's letter about drowning accidents (September 10, p. 798) is timely. I fear that many of the casualties can swim a little, and therein is a danger. A child learns to swim, say, 100 yards in a bath—still water, no waves, no currents—and he will then gaily swim out to sea and may find himself being carried out. Seeing the shore receding, he naturally panics and makes the most strenuous efforts to swim to the beach, exhausts himself, swallows water, and is soon finished.

I suggest children should be encouraged to swim longer distances, slowly, so as never to be out of breath. Certificates could be given for half a mile, which could take 25 to 30 minutes. Now, if a child knows he can swim for half an hour, he is not likely to panic. He can swim easily with the current and give rescuers time to reach him. He must be taught that it is useless to fight the current. Channel swimmers have had to give up when only a mile off shore, when the tide has turned against them. Therefore the suggestions are: (1) Encourage distance slow swimming. (2) Teach that, if in difficulties, not to panic and don't try to back the tide. Further, it is a useful exercise to practise swimming fully clothed and to get your shoes off when in the water. You can't get far with them on.—I am, etc.,

Ipswich CHARLES MILLS.

Treatment of Choriocarcinoma with Cytotoxic Drugs

SIR,—In connexion with the recent article on the treatment of choriocarcinoma with cytotoxic drugs by Dr. Janetta M. McDonald and myself (August 6, p. 426), Dr. D. K. Sambrook (September 3, p. 736) has raised several points which we avoided because of their complexity and because they did not seem to be strictly relevant to the problem of treatment in widely metastasized disease. The difficulties of histological diagnosis, the variable malignancy of trophoblastic tumours, and their unpredictable behaviour are well known. However, it is doubtful whether the mole which exhibits deep invasion of the uterine muscle and of veins should be regarded invariably as "perfectly benign." There are frequent examples[1,2] in the literature of death resulting from such benign tumours, and if there is evidence of progressive disease indicated by a persistent rise in the gonadotrophin titre and evidence of distant embolization then treatment would seem to be indicated. Two of our patients (Cases 1 and 2) did not have histological confirmation of the tumours, although cases with very similar clinical features who came to necropsy were judged to have choriocarcinoma.[3] It would be more correct, therefore, to have described these patients as having "embolic trophoblastic disease," but to the patients with extensive obstruction of the pulmonary circulation by trophoblastic emboli the distinction between benign and malignant may seem somewhat esoteric.

Having rejected spontaneous regression as the cause of the improvement in the condition of the patient he treated with radiotherapy, Dr. Sambrook suggests that this mechanism may have accounted for the remission in four of the six cases we treated with cytotoxic drugs. The incidence of spontaneous regression of metastases following hysterectomy for choriocarcinoma is not known, but Park and Lees[4] reviewed the literature in detail up to 1950 and concluded that it occurred in a small proportion of cases, although the documentation of the original case histories was very incomplete. Our series of six cases is clearly not open to statistical analysis, but it would be surprising if four of them had undergone spontaneous remission. Nevertheless, it is impossible to be absolutely sure that such a process has not coincided with the institution of therapy in an individual case. If, however, it is postulated that a spontaneous regression has been provoked by the removal of the primary tumour, then presumably there should be evidence of improvement in the patient's condition from the time of hysterectomy, and at least a persistent fall in the gonadotrophin titre. In fact, in our series only three of the four cases to which Dr. Sambrook refers underwent hysterectomy and in only two was a tumour identified in the uterus. In all three cases there was clinical, radiological, and hormonal evidence of progression after hysterectomy, and one patient who was in the terminal stages of respiratory failure at the start of treatment was able to get up and about in the ward within one week. It is also difficult to see how spontaneous regression could account for the recurrent rise in the gonadotrophin titre before each course of treatment and the fall which invariably followed.

Dr. Sambrook's conclusion that choriocarcinoma is reputed to be extremely radio-sensitive ought surely to have a more substantial basis than that which he presents. There have been occasional reports of radiological regression of pulmonary metastases following pelvic irradiation, but of fourteen confirmed cases treated by irradiation and reported by Novak and Seah,[5] two were alive after six months and only one after two years. Radiotherapy has been the chief method of attack on metastasized choriocarcinoma for the past forty years, and if it is true that its potential value has been overlooked, may we not ask how much longer is required and what steps are being taken to ensure that a more definite answer will be available after the next forty years?

The importance of trophoblastic tumours in the study of cancer is out of proportion to their relative rarity. This is so, first because of their genetic and immunological considerations, second because of their gonadotrophic activity which provides a readily measurable index of growth, and third because of their susceptibility to inhibition by certain agents, however partial this may be at present. Even so, it is difficult to see how substantial progress can be made in our know-

ledge of rare and complex diseases of this sort until the means exist whereby data concerning them can be collected, verified, and studied in a systematic manner. This is a basic requirement, and we delude ourselves if we think we can make a serious study of these diseases without such facilities. In the U.S.A. there has been a registry of trophoblastic tumours since 1947 (the Albert F. Mathieu Chorionepithelioma Registry), and in addition to collecting data there is an associated histological reference service. An urgent and serious need for a similar registry exists in this country. Perhaps this would be an appropriate activity for one of the Royal Colleges, and the establishment of such a registry would be a logical first step towards providing answers to some important questions.—I am, etc.,

K. D. BAGSHAWE.

St. Mary's Hospital,
London W.2.

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Immobilization of the Arthritic Hip

SIR,—In regard to the hip-splint illustrated by Dr. Michael Kelly, of Melbourne, in your correspondence columns of August 6 (p. 469), I should like to be allowed to point out that this seems to be a version of the hip-splint designed by me over 30 years ago, while I was orthopaedic surgeon to the Bath Orthopaedic Hospital, and used by me with satisfaction all the years I was on the staff of that institution. It was adopted many years ago by the late Mr. Cochrane, of Edinburgh, and continues in use in the Princess Margaret Rose Orthopaedic Hospital.

In regard to the splint illustrated by Dr. Kelly, I would point out that it lacks several very important elements incorporated in my design—i.e., (1) short front and back corsets, which resist the tendency to either lordosis or kyphosis of the spine, so often associated with hip disease; (2) firm padded straps in front immediately above and below the patella in order to resist flexion of the knee and indirectly of the hip; (3) rounding of the lower end of both outer and inner bar for attachment to a socket in the heel of the boot (as for the Thomas's caliper); this controls rotation of the hip, a very important element in hip-disease; (4) two shoulder straps, crossed behind, to ensure good body posture.

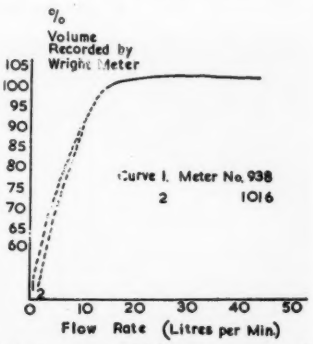
I may add that my splint was initially designed to control tubercular hips after grafting, so as to allow access of sun and air to the skin and massage to the muscles; also, when soft union had occurred, to allow the patient to exercise freely in bed, but to have protection against gravity and slips when ambulant, not to mention the hazards of amateur football. The plaster-spica so commonly used for convalescence after grafts has none of these advantages. The splint can also be used in very carefully selected cases of polio with complete loss of power in one lower limb and part of the trunk, and in such cases it helps to prevent, or greatly reduce, the incidence of scoliosis.

As the splint has to be stoutly built, and hence its weight is not negligible, it seems doubtful whether it would be widely applicable to osteoarthritis; for so often the degeneration is beginning in the second hip, which should not be unduly loaded. For such cases it would probably be preferable to use a very light hip-splint which I recently designed when working in the Transkei, S. Africa, where no splint-workshops are available. It is made out of sheet aluminium cut with a saw to a paper pattern and applied to the outer aspect of hip, trunk, and knee, being held by two shoulder-straps and also a strap at the level of the pubis and two knee-straps, such as already described. The aluminium is only 1/32 of an inch (0.8 mm.) thick, but for heavy subjects two thicknesses can be used. It is easily moulded by hand, but immensely strong in resistance to the indirect strains which reach it when used at the side of a limb. It is useless for direct back or front stresses.—I am, etc.,

Edinburgh 12. M. FORRESTER-BROWN.

The Wright Anemometer

SIR,—The problem of the Wright and other anemometers was thoroughly discussed during the symposium on pulmonary ventilation at Leeds two years ago.[1] A respirometer of this type is recognized to be unreliable where low flow-rates are being measured. The manufacturers claim[2] that the Wright anemometer is reasonably reliable down to flow rates of 5 litres/min. For some time now, in this department, we have had experience of this instrument, and find it most useful in measuring expired minute volumes at the flow rates commonly encountered during clinical anaesthesia. Recently, however, we found it necessary to check its accuracy at flow rates less than 50 litres/min.



Tests on two Wright anemometers at low flow-rates.

Two Wright anemometers were tested in series with the gas-meter (type C.D.1) manufactured by Parkinson and Cowan (0.5% error up to flow-rates of 60 litres/min.). The different flow-rates were obtained from a variable pump. If one accepts an accuracy of 90% of the reading on the calibrating apparatus as reasonable, then it is seen that this instrument is unsuitable for use at flow rates of 12 litres/min. and below (see Fig.). These findings may be of some interest to anaesthetists presented with the extremely difficult problem of monitoring gas-flows at these low rates. At the same time, we do not wish in any way to detract from the value of this anemometer in measuring more normal flow-rates during routine clinical work.

I am indebted to Mr. T. Duggan, physicist, Western Regional Hospital Board Physics Department, Glasgow, for his assistance in this investigation.

—I am, etc.,

DONALD CAMPBELL.

University Department of Anaesthetics,
Glasgow Royal Infirmary,
Glasgow.

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"Winkle-picker's" Disease

SIR,—Tenosynovitis of the long extensor tendon of the hallux is a relatively uncommon condition. It is usually associated with the dorsal osteophyte-formation of hallux rigidus. The introduction of the new style of women's shoes, nicknamed "winkle-picker" because of its sharp point, has been responsible for this lesion becoming more prevalent. The shoe differs from its predecessors in that the proximal open rim of the toecap lies much more distally than previously, and therefore crosses the big toe just beyond the metatarso-phalangeal joint (Fig. 1). Irritation from this rim can produce reactive tenosynovitis of the extensor tendon.

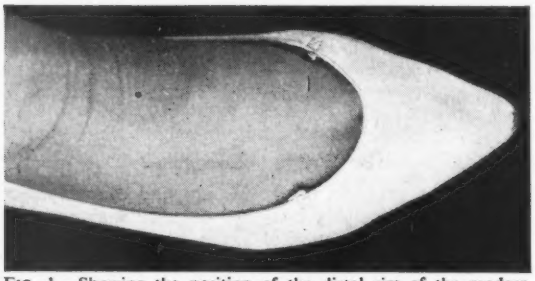

FIG. 1.—Showing the position of the distal rim of the modern court shoe.

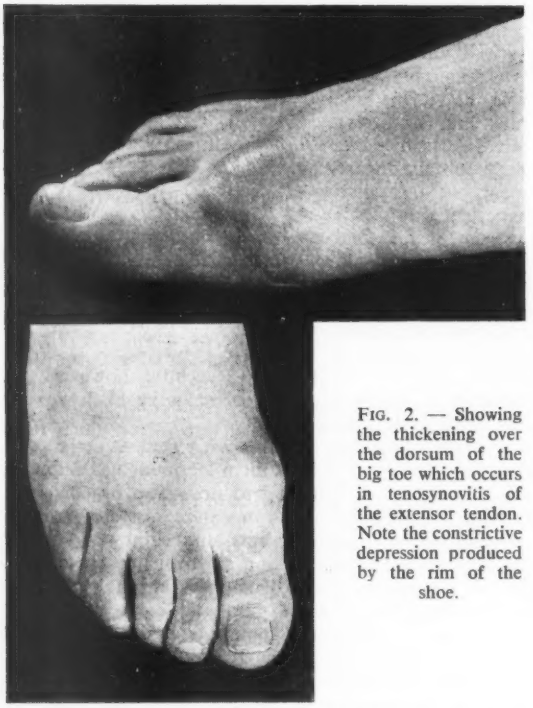

FIG. 2. — Showing the thickening over the dorsum of the big toe which occurs in tenosynovitis of the extensor tendon. Note the constrictive depression produced by the rim of the shoe.

A 22-year-old girl presented with a history of a gradually increasing swelling over the dorsum of the right foot near to the big toe for the past two months. This was particularly painful when she wore shoes of the new style. There was no history of injury. Examination showed the swelling to be confined to the long extensor tendon of the big toe (Fig. 2). There was no loss of movement in the metatarso-phalangeal joint, nor was there any osteophyte formation over the dorsal surface. *X*-rays of the foot were normal and the E.S.R. was 9 mm./hr. (Westergren). Tenosynovitis of the long extensor tendon of the hallux was diagnosed and the patient advised to wear low-heeled shoes of the ordinary lace-up type. When seen two weeks later the condition had almost completely settled.

Tenosynovitis of the extensor hallucis longus tendon is seen from time to time, either in association with hallux rigidus, or as a result of irritation when breaking in a new pair of shoes. The condition is as common in men as in women, and the thickening in the tendon sheath is directly associated with the source of irritation. Four cases have been seen by the author in the last twelve months in women who have just taken to wearing the latest style of court shoe. The clinical appearance differs from the usual variety of this condition in that the swelling over the tendon is much more marked and is proximal to the site of shoe pressure. It appears that the rim of the toe-cap acts as a constricting force and produces a reaction in the proximal part of the tendon, as seen in tenovaginitis stenosans. In three of the cases the symptoms resolved after a change of footwear. In one case the condition was cured by a local injection of hydrocortisone.

I am indebted to Mr. Whitley, of the Photographic Department of the Institute of Orthopaedics, for producing the illustrations.

—I am, etc.,

Royal National Orthopaedic Hospital, Stanmore. J. N. WILSON.

Potentiation of Pethidine

SIR,—Dr. J. Charles Shee's article on "Dangerous Potentiation of Pethidine by Iproniazid, and its Treatment" (August 13, p. 507) prompts me to recall an unexplained and totally unexpected death of a patient who had been the subject of surgical intervention the day before he died, prior to which he had been receiving routine "nardil" (phenelzine) administration. Following the operation he was given two injections of pethidine, totalling 150 mg. in all, one at 4.30 p.m. and one at midnight, but in addition he had received morphine gr. 1/6 (11 mg.) at 2.30 p.m. Before his death he became extremely restless with hyperpyrexia and cyanosis. A post-mortem examination revealed no adequate cause for death, and there was no evidence of terminal pneumonia. At the time I speculated as to whether or not the pethidine had been potentiated by the phenelzine.

His condition had, in fact, shown no cause for anxiety whatsoever until his first dose of pethidine at 4.30 p.m. If now it be assumed that possibly here was a case of pethidine potentiated by phenelzine the fatal outcome following the second injection at midnight is explained.

—I am, etc.,

Hill End Hospital, St. Albans, Herts. HAROLD PALMER.

Henna for Intestinal Moniliasis

SIR,—Henna (*Lawsonia alba*) is grown in Egypt, India, and many subtropical countries for commercial purposes. The dried, ground leaf is used as a cold poultice which, when applied to the skin, leaves a red-brown stain. It is used for decorative purposes in various ritual ceremonies as well as a remedy for many skin affections, the majority of which are known to be fungal in origin. I have used henna successfully in the treatment of intestinal amoebiasis.[1] A year ago, faced by a shortage of nystatin[2 3] in this country, I used henna in four cases of intestinal moniliasis with good results. All these patients had taken oral oxytetracycline for a prolonged period and had developed diarrhoea and mild-

grade fever, which persisted long after the drug was stopped. The complaints and findings in these patients were similar and are illustrated in the following case history.

A European female, age 45, was well until three months ago, when she had "'flu," with cough and fever. Her doctor gave her oral oxytetracycline, 500 mg. every six hours, daily intramuscular injections of vitamin-B complex, and a codeine-containing cough mixture. By the seventh day, though the cough was better, she began to have frequent stools, tenesmus, and mild fever. By the fifteenth day she was having about six stools daily with marked abdominal distension, tenesmus, and was feeling very tired. Her treatment was changed to chloramphenicol, 500 mg. six-hourly, and two "entero-vioform" (iodochlorhydroxy-quinoline) tablets three times a day, but the symptoms persisted and she began to lose weight rapidly. She was seen by several doctors and had had a variety of dietary and medical treatments with no result.

When I first saw her she had been ill for about three months and her weight was down by 12 kg., and she was having four to eight loose stools every 24 hours. Clinical examination revealed no abnormality apart from a distended tender abdomen and general wasting. The blood picture showed a microcytic hypochromic anaemia (Hb 7 g./100 ml.). Stools examination showed a rather watery, malodorous stool with excess mucus; microscopy showed excess R.B.C.s and leucocytes, and much undigested starch and vegetable matter; no parasites were found. Sigmoido-scopy showed an angry red granular mucous membrane which bled rather easily, but no ulcers were seen. Scrapings of the mucous membrane showed no amoebae, but numerous fungi, identified as *Candida albicans*, were seen on staining the specimen with methylene blue. Repeated stool examination for fungus was strongly positive. Nystatin was not available, so she was given 2 g. of henna powder in cachets three times daily after meals, and was put on a diet low in carbohydrates and fat.

She began to improve on the fourth day, and by the tenth day she was afebrile and out of bed, having two stools daily with very little discomfort. Stool examination for the fungus was negative on the seventh day and thereafter. The henna was continued for one month. At the end of the month the patient was well and gained 5 kg. in weight. When seen again three months later she was normal in every respect, had gained 17 kg. in weight, and was now dieting to stop the weight gain. Repeated stool examination and sigmoidoscopy were negative.

The other three cases gave more or less similar histories of prolonged antibiotic therapy, followed by a two months diarrhoea, tenesmus, distension, and loss of weight. The response to henna therapy was similar in these cases.

With the increasing, indiscriminate use of antibiotics in this country we are beginning to see the various complications of their use which have been described in Europe and the States. Fortunately these are still rare, as the cost of these antibiotic drugs is prohibitive to the majority of patients. It is probable that the incidence of intestinal moniliasis after oral antibiotic therapy is commoner than is suspected, and that the milder affections which cause few or no symptoms pass unnoticed. Henna contains multiple dyes, the chief of which is 3-hydroxynaphthoquinone.[4] An analogue, 5-hydroxynaphthoquinone,[5] which is present in the black walnut, is known to be a strong fungicide.—I am, etc.,

Department of Medicine,
Cairo University, Egypt. SAID M. TALAAT.

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Books on Brucellosis

SIR,—Both Professor L. P. Garrod (August 27, p. 651) and Dr. I. M. Librach (September 10, p. 806) are wrong. It is true that my monograph preceded Sir Weldon Dalrymple-Champneys's book by a few weeks, but the first publication in this country was that of M. L. Hughes, *Mediterranean, Malta or Undulant Fever*, in London as long ago as 1897.

Anyone who can get hold of this excellent monograph should read it. It is remarkable for the clarity of its clinical descriptions, the shrewdness of its observations, and its appositeness to present-day conditions. The author was a surgeon-captain in the Army Medical Corps, who was later killed in action in the Boer war. Had he lived he would undoubtedly have reached the top of his profession, and it is probable that this fascinating disease would not have suffered from so much unfortunate neglect. His words on first meeting with the fever in Malta could well be applied to conditions in this country to-day. "How much there was to learn and how little to guide anyone in the study of this important fever."—I am, etc.,

Bath. HUGH WALLIS.

Doctors' Letters

SIR,—I would like to add just a little to Dr. John Fry's excellent letter (July 30, p. 384). Many complaints are consistently heard about the general practitioner's letter to hospital, but in a short eighteen months in general practice I have noticed certain trends in the hospital replies, particularly from the intermediate hospital medical officer, from which I conclude that often the practitioner's letter, good or bad, is being unread and/or disregarded. As a result a G.P.'s home treatment may be duplicated by hospital. The patient may even return to the surgery from hospital with the practitioner's note, a knowledge of its contents, and resulting anguish and annoyance. Often when one encloses a sheaf of documents from the patient's medical envelope to a hospital department with an explanatory note attached, it is returned still pinned to the documents instead of being detached and filed with the hospital case records for future reference.

Hospital departments are overworked, and the staff often harassed to the limit, but that is no adequate excuse for overlooking the letter from the patient's practitioner.—I am, etc.,

Milngavie, Dunbartonshire. D. SUTHERLAND MUNRO.

Blue for Poison

SIR,—Now that so many drugs enter the home in the form of tablets that bear some resemblance to sweets, the risk of a child's eating what may be deadly poison is increasing. The curiosity of a child has no limit, and nothing short of locking medicines away, and then removing *and hiding* the key, can avail against it—and this is a sterile policy of perfection when it has to be applied by an overworked and harassed mother.

There is, however, one device that has not yet been tried and would cost nothing to adopt. No natural foodstuff is blue; it is true that some have a bluish tinge, but literally none is bright blue. Red and green lights are now accepted everywhere as meaning no and yes respectively, so why not adopt bright blue as the exclusive label of poison? The co-operation of all makers of eatable artifacts to ban that colour would be necessary, but they would not be deterred by competition,

for all could be willing to agree. The essential corollary to this is that every child should be told, again and again from its earliest days until fully conditioned, the maxim: "Never eat anything blue," the brevity and dactylar rhythm of which would help to drive it in. This plan is not perfect, for there are some who cannot recognize blue, but it would be a powerful aid to safety of life.—I am, etc.,

Edinburgh 5. G. STRUAN MARSHALL.

Vale of Leven Hospital

SIR,—My attention has been drawn to a note about Altnagelvin Hospital, Londonderry, Northern Ireland, in the photographic supplement (p. 7) to your Special Hospital Number of September 10. In this note it states that Altnagelvin Hospital is the first completely new hospital to be finished in the United Kingdom since the war. I trust you will not mind me drawing your attention to this misstatement, as the Vale of Leven Hospital, Alexandria, Dunbartonshire, was the first complete new hospital to be built in Britain since the war. This hospital was given a great deal of publicity at the time, and, for your records, the hospital was opened in December, 1955.—I am, etc.,

Dunbarton. J. CAMPBELL,
Secretary,
Vale of Leven Hospital.

*** We apologize for this oversight.—ED., *B.M.J.*

Imaginary Poverty

SIR,—Some of your readers may be interested in an early reference[1] to imaginary poverty:

"On Sunday, March 30, I found him at home in the evening, and had the pleasure to meet with Dr. Brocklesby, whose reading, and knowledge of life, and good spirits, supply him with a never-failing source of conversation. He mentioned a respectable gentleman, who became extremely penurious near the close of his life. Johnson said there must have been a degree of madness about him. 'Not at all, Sir (said Dr. Brocklesby), his judgment was entire.' Unluckily, however, he mentioned that although he had a fortune of twenty-seven thousand pounds, he denied himself many comforts, from an apprehension that he could not afford them. 'Nay, Sir (cried Johnson), when the judgment is so disturbed that a man cannot count, that is pretty well.'"

—I am, etc.,

Edgware, Middlesex. A. T. RODEN.

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[1] Boswell, J., *The Life of Samuel Johnson*, Everyman edition, 1906, **2**, 439.

Jewish Medical Ethics

SIR,—My attention has been drawn to Prof. Arnold Sorsby's review of my book, *Jewish Medical Ethics*, (August 27, p. 652). Readers of the review may get the false impression that my book is a manual on Biblical medicine, or a recapitulation of the standard works by Preuss and Katzenelsohn on medicine in the Bible and Talmud. In fact, it is nothing of the kind. It surveys the attitude of Judaism, as well as of Christian and other religious teachings, to moral and religious problems in medical practice. In this survey the *medical* data found in the Bible constitute only a very small and insignificant fraction of the sources consulted.

My main concern was to analyse the *moral* views of the major faiths on various medical procedures which may impinge on religious principles, and I dare say that many of your medical readers will disagree, as I do, with your reviewer's opinion that these views—as historically investigated in my book for the first time—have no "valid message to-day." Whether, and under what circumstances, such considerations as the sanctity of human life (involved in euthanasia and abortion), the inviolability of the dead (in necropsies), the exclusiveness of the marriage bond (in artificial insemination), the virtue of truthfulness (in informing patients of their condition), etc., may be violated, even for medical ends, raises moral, not medical, questions. For religious people the answers can only be found in the realm of religion, not of "medical folklore," and its definitions of right and wrong, I submit, are as relevant to-day as they were in the days of the Bible.—I am, etc.,

IMMANUEL JAKOBOVITS,
Rabbi,
New York 21, U.S.A. Fifth Avenue Synagogue.

Church Service for Doctors

SIR,—May I, through the courtesy of your correspondence columns, once again draw the attention of your readers to our Special Service for Doctors, which is to be held in All Souls' Church, Langham Place, W.1, this year on Sunday, October 16, at 11 a.m. We greatly value our link with the medical profession, and have been encouraged by the support which they have given to these services during the last eight years. Sir Arthur Porritt, P.R.C.S., and Sir James Paterson Ross, Bt., have kindly agreed to read the lessons.

This year, for the first time, a buffet lunch is being arranged after the service at the Royal Society of Medicine, through the kind co-operation of the secretary, Mr. R. T. Hewitt, at a cost of 7s. 6d. a head. We shall be happy to reserve seats in church for doctors and members of their family who apply for tickets in advance, and also to issue tickets for the buffet lunch. Application (stating number of tickets required, and enclosing remittance for the luncheon) should be made to the Church Secretary, All Souls', Langham Place, W.1, by Thursday, October 13.—I am, etc.,

JOHN R. W. STOTT,
Rector,
London W.1. All Souls', Langham Place.

POINTS FROM LETTERS

Gentlemen Boxers' Brains

Drs. F. B. BYROM and P. M. DANIEL (Institute of Psychiatry, The Maudsley Hospital, London S.E.5) write: The particulars of punch drunk boxers which Colonel J. W. Graham (September 10, p. 806) seeks can be found in the publications of Critchley,[1] who in 1957 had collected 69 cases of neurological disease in boxers, mostly examples of the punch drunk syndrome, and of many other writers since Carroll[2] first coined the term.

REFERENCES

[1] Critchley, M., *Brit. med. J.*, 1957, **1**, 357.
[2] Carroll, E. J., *Amer. J. med. Sci.*, 1936, **191**, 706.

Adiposity

Dr. L. M. SHIRLAW (Romford, Essex) writes: As a reluctant owner of the adipose organ, I have read Professor A. Kekwick's article on adiposity (August 6, p. 407) with great interest and considerable incomprehension. If I interpret his findings correctly, 90% of the population (as 10% only suffer from obesity) manage to survive without this organ. My own hypothesis is that adipose tissue is a vestigial remain. In prehistoric times early man roamed the countryside during the warm weather, living on the available foodstuffs and storing a reserve underneath the abdominal skin, to be used during the inclement weather, when he hibernated in caves living on his own fat.

Obituary

Sir GORDON GORDON-TAYLOR, K.B.E., C.B.

M.D., Hon.LL.D., Hon.Sc.D., M.S., F.R.C.S., Hon.F.R.C.S.Ed., Hon.F.R.C.S.I., Hon.F.A.C.S., Hon.F.R.C.S.(Canada).

The obituary of Sir Gordon Gordon-Taylor was published in the *Journal* of September 10 (p. 807).

Mr. DAVID PATEY writes: Everyone who met Gordon-Taylor, even if only briefly, was captivated by the charm of his vivid and magnetic personality. With his patients, his kindness and courtesy at once put them at their ease, and the relationship quickly became one of confidence. He liked and was interested in people, and he had the gift of communicating this friendly interest not only to patients but to everyone else he met, a gift which was magnified by a remarkable memory both for people and events. But with all his charm and friendliness there was a reserve of dignity which was never forbidding, but which even his closest friends did not penetrate. Those who worked for him became his devoted slaves and dedicated followers, and a measure of his influence is the extent to which his ex-house-surgeons achieved staff appointments not only at Middlesex but also in teaching and other leading hospitals at home and in the Commonwealth. The legitimate criticism was sometimes made that all Gordon-Taylor's geese were swans; on the other hand, he stimulated more than one goose to try to sprout a few swan's feathers.

Almost certainly no other surgeon can have had so many surgical friends in all parts of the world. His main friendships were naturally but not exclusively in the Commonwealth and the English-speaking world. It would be impossible to measure the enormous amount of good will generated for Britain in India and Pakistan from the fact that the chief mentor of their postgraduate surgical students in Britain exemplified so splendidly all that was best in the traditional picture of an English gentleman. A letter of introduction from Gordon-Taylor was a privileged passport in any surgical centre of North America, and in Australian and New Zealand surgery he was an uncrowned king. Rumour has it that a hint from Gordon-Taylor in favour of a candidate for election to the Council of the Royal College of Surgeons of England was worth as many votes as there are Australian and New Zealand Fellows.

As a surgeon, Gordon-Taylor's most striking virtue was courage. It required courage to advise partial gastrectomy as a standard treatment for duodenal ulcer at a time when the general climate of surgical as well as medical opinion was that the operation was unjustifiably mutilating; it required courage to perform a hindquarter amputation forty years ago with the limited anaesthetic and resuscitative facilities then available. To these and other similar enterprises he brought cool judgment, calculated deliberate action, and a superb knowledge of anatomy. In his early days on the staff at Middlesex he was assistant surgeon to Sir Alfred Pearce Gould and to Sir John Bland-Sutton, both of whom he admired greatly. To Bland-Sutton, operating had something of the nature of a glorious cavalry charge, and to the end Gordon-Taylor tended to preserve something of this attitude when, on occasion, he set out like a knight in shining armour to rescue some unfortunate sufferer from what he considered to be the inertia of the physician or the over-enthusiasm of the radiotherapist. He also found the Bland-Sutton philosophy valuable during the heavy and hectic days of the first world war, when he and other brilliant young surgeons in the casualty clearing stations of the Western Front established that patients with penetrating wounds of the abdomen can be saved by bold active surgery conducted with dispatch.

The surgeon who mainly influenced him, however, was undoubtedly Moynihan, who, when Gordon-Taylor was a young man, was establishing in this country the tradition of a scrupulously careful technique of operating, the tradition which, merging with the similar tradition established in America by Halsted, has led to the modern technical triumphs of surgery. Gordon-Taylor did not merely passively follow; on the contrary, he played a big part in enabling modern scrupulous techniques to become established by his encouragement of improvements in supportive and resuscitative methods and of advances in anaesthesia. His experience of blood transfusion during the first world war convinced him of its importance for elective surgery, and after the war he established at Middlesex, and paid for personally, a blood-transfusion organization. Later he welcomed and encouraged the work of Marriott and Kekwick in the development of drip transfusion. His most notable contribution to anaesthesia was with Apperley and Hillman in the application of splanchnic anaesthesia, an important half-way house to modern relaxant anaesthesia in abdominal surgery.

Gordon-Taylor's knowledge of anatomy enabled him to apply Moynihan–Halsted techniques to many parts of the body. He tackled vigorously the problems of carcinoma of the lip, tongue, jaws, and oropharynx at a time when radiotherapy in these regions hardly existed, and moreover of necessity carried out himself the operations of plastic reconstruction. Owing to the routine practice of prophylactic block-dissection of the neck in these conditions, hardly a week passed by without seeing one of these operations on his list. His other major interest was abdominal surgery, which at that time constituted the advancing edge of surgery and for this reason alone would have attracted him. Here his most notable contribution was to carry forward the work of Finsterer, of Vienna, in establishing the rational and correct treatment of continuing bleeding from a peptic ulcer—namely, to operate and control the bleeding at source. This conclusion to-day seems so obvious that it is difficult to realize the opposition it aroused among leading gastric physicians, often supported by seemingly convincing statistical proof, on the grounds that operation was too dangerous and in any case not as effective as the routine administration of morphine.

No account of Gordon-Taylor's surgical contributions would be complete without mention of hindquarter amputation, which, almost entirely owing to his advocacy and practice, has become a routine operation of surgery. The operation satisfied all aspects of his philosophy of surgery. He was able to rescue many patients abandoned as untreatable or treatable only by palliative agents; he was able to operate in bold broad sweeps worthy of a Bland-Sutton and scoff at the dilatory tactics of surgical tortoises; but at the same time he was always careful to provide himself with a team of skilled and experienced assistants who concerned themselves with the exact details of the operation, and to make full use of all the resources of modern anaesthesia and supportive therapy.

Gordon-Taylor was interested in surgery almost entirely in its primary purpose as a therapeutic weapon, and, unlike his colleague Sampson Handley, was little concerned with its possibilities in biological and pathological discovery. Unlike, too, his colleague Webb-Johnson, he was uninterested in hospital and medical-school organization and administration, and rarely attended committee meetings at Middlesex. He was if need be a good didactic teacher, but preferred the informal group discussion in the ward or operating-theatre. Towards physiology he affected a bantering attitude, and he delighted in short-circuiting an obstructive jaundice by anastomosing the gall-bladder with the stomach, and in pointing out that the results were just as good as the more physiological anastomosis with the upper small intestine. But, through his colleagues and assistants, he always made the fullest use of any application to surgery of advances in physiology, biochemistry, and pathology.

Finally, mention must be made of his gifts as a writer and orator. Not for him either in the written or the spoken word the simple unadorned prose style that is to-day fashionable, probably a result of our scientific age. Soaked as he was in classical culture and the humanist tradition, his phrases were rich in imagery and metaphor, and there was hardly a formal paper or speech into which he did not introduce a Latin or Greek quotation, which he usually did

not insult his audience by translating. He would have been at home linguistically in the House of Commons of Burke. In lighter vein, he had a great fund of anecdotes, many apocryphal, about the surgical figures of the past, usually related with an added sauce of piquancy.

Of his many and varied qualities, the ones that will chiefly remain in memory will be the dedicated surgeon, the lovable personality, and the spirit of perpetual youth.

Sir GORDON BELL, K.B.E., F.R.C.S., writes from Dunedin, New Zealand: I find it difficult to write in measured terms of Gordon Gordon-Taylor. When I saw him last three years ago in London he was looking forward to his 80th birthday and the approaching completion of a round hundred of hind-quarter amputations: indeed, he appeared to bear an aura of indestructibility, for his mental qualities shone as brightly as ever and his pedestrian prowess was unimpaired though perhaps the pace had slowed. He came of a long-lived stock and doubtless his Aberdeenshire background contributed to his toughness. And now those crowded London streets he loved so well have claimed him, and those long-trodden paths will know that tall, trim, erect, slightly old-fashioned figure no more.

I met him first in 1916 during the Battle of the Somme, and thereafter till the end of the war our paths frequently crossed in the clearing-station zone, and my regard and affection for him steadily grew. During the Passchendaele fighting of 1917 I was attached to a forward group of clearing stations at Brandhock, near Vlamertinghe, and visiting surgical teams included Ernest Miles, C. H. Fagge, Rock Carling, and Gordon-Taylor. To live and work with older men of such high quality was a privilege and an education to juniors like myself; and of them all Gordon-Taylor stood pre-eminent, partly because of his surgical distinction and partly because of his innate kindliness, sympathetic understanding, and appreciative attitude towards the younger men: in short, he was like a respected and much admired elder brother, someone to emulate. It was his idea that the brotherhood of C.C.S. surgeons should be carried into civil life, and he envisaged a travelling club which would cover most of Great Britain, but for various reasons this fell through and we went our various ways.

Later on he came to New Zealand and Australia as anatomist to several visiting teams of examiners for the Primary Fellowship. Then in 1945, accompanied by his devoted *aide*, Lambert Rogers, he visited us on a good-will tour. Here and in Australia this was more in the nature of a royal progress, and I am sure the warmth of his welcome must have afforded an intense gratification to his modest and responsive heart.

No British surgeon was better known to us and none could have provided a happier link between the old and the new. The key to his supremacy lay, as it did in those far-distant war days, in his obviously genuine sympathy and understanding of the problems of younger men, and no one was quicker to give praise when due. His friendships ranged from contemporaries down the scale to examination candidates who became his friends overnight and sought his advice in their careers.

I write this as a personal tribute to a dear and ever kind friend, and I know that it expresses the feelings, in some part at least, of many others. If fate denied him the Woolsack, as he termed it, he had a more solid satisfaction in the affectionate regard of countless friends and admirers.

P. W. writes from St. Andrew, Jamaica: Gordon-Taylor was one of the greatest of the great generation of surgeons, the pioneers of modern surgery, and he was surely the best-loved surgeon in the world. There is no one who has been his patient, his pupil, or his colleague who does not mourn him. He left an indelible mark on his registrars and house-surgeons, and I was lucky enough to be one of them. Imbued with the spirit of surgery, his enthusiasm was so contagious that all who worked for him came under his spell, and to the end of their lives will be compelled to emulate his dedication to his patients and his craft. But "G.-T.," great surgeon though he was, will be remembered even more for his devotion to the young men of surgery. He became the loyal friend of his former assistants and never ceased to help and encourage them—their debt is so much greater than they can even think of repaying. As he became older he gave his time increasingly to succeeding generations of budding surgeons. They came to him for advice from Australia, India, Nigeria, the whole Commonwealth, and he gave it unsparingly; and, more than that, he seldom failed to fix a man up with the right course or find him the right job (and to this end he bullied his colleagues unmercifully). What better memorial can a man have than that his spirit should live on not merely in one but in three of four succeeding generations?

V. B. G.-A. writes: Others will write of his courage and skill, but it is as a clubman that I would speak of "G.-T.," for almost daily he would jauntingly stride from his flat in Harley Street to a meal at the Oriental Club, with as often as not some Antipodean friend, though, as he would say with a twinkle, if there were ladies present they and he would prefer the Ritz. At the club there was nothing he liked better than to be joined by one of us and then memorize about cabbages and kings he had met all over the world, but particularly the Far East as Royal Naval consultant or examiner. If given half a chance or slyly egged on he loved to spell yarns of Bland-Sutton and the Baron, keeping us in fits of laughter over incidents in his long career at the Middlesex, all the time chuckling to himself as his pawky humour overflowed. But never have I heard him say a bitter or sorry word about his own luck. Indeed, apart from his love of meeting and corresponding with old friends the thing that gave him most pleasure was to speak of ex-housemen of his all over the Empire who had reached eminence, and I am sure that nothing so enthralled him as to write one of his wonderfully legible letters of congratulations to some old coachee, or student, or war friend who had achieved honour. At the club we shall all, including Kathleen, Harris, Piercy, and Ashcroft, deeply miss his welcoming smile and the charm of his great humility, for "Here was a Caesar! Whence comes such another?"

Professor PAUL MARTIN of Brussels, Secretary General of the International Society of Surgery, has sent this telegram to the Society's British members: Deeply moved by the death of Sir Gordon Gordon-Taylor. The officers of the Société Internationale de Chirurgie send you their appreciation for the devotion manifested by our most distinguished Membre d'Honneur to the purposes of our Society. Sir Gordon will live for ever in the hearts of our members.

Sir HAROLD GILLIES, C.B.E., F.R.C.S.
Hon.F.R.A.C.S., Hon.F.A.C.S.

The obituary of Sir Harold Gillies appeared in the *Journal* of September 17 (p. 866).

T. P. K. writes: No one who enjoyed the privilege of working in association with Sir Harold Gillies could avoid being inspired and stimulated by his almost boyish enthusiasm for his work, by his originality of thinking, and by his superb craftsmanship. His patience was proverbial, and characteristic of this was his readiness to undo twenty or more scrupulously inserted sutures if, in the final stages of an operation, he saw some more advantageous way of approximating the skin edges concerned. More than once he asserted that this was the true test of a surgeon's temperamental suitability for plastic work.

It was my good fortune to come under his influence in the early days of his spectacular career as a reconstructive surgeon when, posted as "plastic surgeon" from a surgical specialist appointment in France in March, 1919, I found myself in an atmosphere described by someone as one of "intellectual fervour and surgical enthusiasm" at the Queen's Hospital, Sidcup. This was indeed a sudden and complete change from work on fractured femurs abroad to a hospital at home filled to overflowing with face and jaw injuries. It took only a few weeks under Gillies's expert guidance to be rendered capable of tackling at least some of the difficult problems which our cases presented.

It was customary in those days to have plaster casts made of all the more seriously injured men, and it was on these casts that we juniors in the British section of the hospital worked out procedures for submission to our chief, for his criticism, approval, or emendation. These consultations took place in a small office, not more than 8 by 10 ft., which was Gillies's sanctum sanctorum, and in which he spent so much of his time thinking and planning when he was not busy operating. Criticism was sometimes cruelly destructive of our immature plans, but it was always kindly presented and followed by constructive advice. It was certainly an advantage to be able to discuss things freely, unhampered by the presence of the patient himself.

To Gillies must be given credit for introducing so many of those things which no modern plastic unit would dream of being without. Dental collaboration was provided on the spot, and dental surgeons, imbued with the same enthusiasm as the surgeons, were always at hand for discussion and assistance.

It was at Sidcup that I first saw the enormous value of clinical photography and of "continuation of treatment" beds. These latter had been chosen by Gillies in a near-by hospital where full supervision by the surgeons could be given. They relieved the nursing staff, increased operation output, and, above all, gave a sense of freedom to patients well enough to be up and about between stages of treatment.

When the bulk of the post-war work was finished, most of the surgeons returned to their pre-war specialist posts, but Gillies, with characteristic courage and vision, decided to continue doing reconstructive work, and by this time civilian cases were beginning to come his way. He took consulting-rooms in London, and I rented a room from him which made it possible to continue a close association which lasted in all for 11 years. We worked together on his cases while I continued doing general surgery in two hospital appointments, still uncertain whether plastic surgery as a specialty could provide a livelihood. How unfounded were my doubts. Work began to pour in, sometimes direct but most frequently from surgeons who willingly renounced cases they felt they could not treat satisfactorily themselves.

More than once Gillies raised the idea of developing a special private hospital, and about this time he discussed the possibility of having an aeroplane at the ready, complete with nurse, anaesthetist, assistant, and instruments, to fly at short notice to the scene of a hunting accident or the like. Until the London Clinic opened—and by this time I was working independently—operative work was troublesome in the extreme, for heavy bags of special instruments and equipment had to be transported from one nursing-home to another as facilities for admission of patients were obtained. The anaesthetist and assistant often had a trying time in those days, for Gillies, with the true artist's temperament, hated being ruled by the clock.

Teaching hospitals were slow to establish plastic units, but gradually the more enlightened ones saw the need, and appointments were made. In the meantime Gillies's services were in great demand in other hospitals in London and the provinces, and the load he carried for several years was a tremendously heavy one. In spite of this he found time for golf, for fly-fishing, and, later, for painting, and to all these he brought the same energy, enthusiasm, and originality of thought and action. Few will know that he devised (and I believe patented) a rotating car seat giving the driver easier egress and entry. Few, too, will know that he performed on the violin with something more than amateur proficiency.

He was responsible for the formation of the British Association of Plastic Surgeons, and became its first president. He was a good friend to all who served him, and everyone in the specialty will miss him sorely. He was indeed a man of many parts the like of which we shall not see again.

His was a full life, restoring morale to countless disfigured or disabled men, women, and children, while at the same time giving his services unremittingly at home and abroad to the specialty he had pioneered. He went to his rest, as I am sure he wished to do, still in harness. Our sympathetic thoughts go out to his widow and to his children, to whom it must be a great consolation to know that he will be remembered in deepest gratitude by those practising the specialty he created and by the innumerable patients to whom he brought happiness.

Mr. PATRICK CLARKSON writes: Men as versatile as Gillies are not usually found in the discipline of medicine. His eminence in sport as well as his professional prestige made him for over forty years a member of a bigger and wider world than that enjoyed by most consultants. Indeed, it is in that wider world that memory and recognition of his contribution to the British Army was always keenest. The profound effect on the morale of the British Army which his success in caring for the wounds of the face and jaws had at one of the gravest times of the first world war has not always been remembered in medical circles to the extent it is by the lay public. By the end of that war he was an international figure, and rightly so. His book, *Plastic Surgery of the Face*, based upon his methods of reconstruction after missile wounds, established the specialty of plastic surgery in Britain.

He was a founder and chief pioneer in the renaissance of a vigorous and expanding branch of surgery, and few surgeons have discharged heavier clinical responsibilities with greater success and originality. Those concerned with the treatment of battle and air-raid casualties in the second world war will always find it difficult to understand how Gillies and his co-workers at Sidcup successfully could accept convoys of up to 500 face and jaw wounds, and, always testing and trying new methods, working with negligible ancillary services, produce results which compare at least favourably with the best that were obtained under altogether better conditions, in terms of equipment, ancillary services, and load of work, in the second world war, during which he himself again worked long hours in the operating theatre at Basingstoke treating Army and Navy casualties and civilians injured in air-raids.

He was a consummate teacher. His pre-operative planning clinics were as unique as they were essential to successful results. In these the use of exact patterns of flap and pedicle, and the deliberate marking on the skin of the exact site and length of the incisions, all made their deep teaching impact. Above all, it was the timeless patience with which these pre-operative sessions were conducted that most characterized them. In many hundreds of hours in the theatre, assisting or watching Sir Harold at operations, I never saw a hurried or rough movement. He was consistently gentle and accurate, the movements of his hands with instruments being deft and beautiful. The operation was conducted regardless of time and solely directed towards the best possible end-result. He was regardless of the length of the operating-list, regardless of the time that any meal might be due, and certainly regardless of any committee that might have been arranged. Absolute accuracy of suture and complete gentleness in the handling of tissues were the two things that were always taught. A special feature of his instruction to a new pupil would be the fateful words, "Take them all out, dear boy," as the last of a hundred sutures had just been inserted, but without that exact edge apposition upon which he insisted and which he himself always so beautifully exhibited. He was the first surgeon I ever saw who consistently practised what he taught, about the importance of the application of dressings to success. He always himself applied the pressure dressing and the bandage which contributes so much to the success of reparative surgery. Gillies's teaching influence was enormous. It can be reasonably claimed that all plastic surgeons in Britain to-day are first, second, or third generation pupils of Gillies. Few British surgeons can ever have trained so many consultants in charge of surgical services abroad.

He was generous in his attribution of credit to others, and took particular pride in the accomplishments of his pre-war colleagues, McIndoe and Mowlem. His attitude

towards the introduction of the tube pedicle was typical. He always insisted upon the fact that Filatof, the ophthalmologist in Odessa, had first introduced it about a year before he did. But it was of course Gillies who was responsible for the development of this method of tissue transfer, which in certain cases alone can save a leg, restore function to a hand, or effect restoration of lost features.

His generosity was consistent and great to those with whom he worked. He not only taught his pupils their craft but very largely set a number of them up in practice. His fertility of mind and originality of thought were consistent until the end. There was scarcely a problem in reconstructive surgery in which he had not contributed some original ideas. The basic qualities which he brought to the consideration of every problem were those of fertility and originality, but he combined them with quite extraordinary patience—in the pre-operative preliminaries, at operation, and in his efforts to obtain the best possible result. His patients understood this, and rightly trusted him implicitly. There is no other book on reconstructive surgery so comprehensive, so authoritative, or so influential as his *Principles and Art of Plastic Surgery*, written with Ralph Millard in 1957. It is a measure of the man that he was able to produce this massive crystallization of his life's work while in his mid-seventies.

Of slight stature, he was a quiet man of unfailing courteous demeanour. His character contained strains of genuine humility, and he had a strong sense of the ridiculous and a continuing enjoyment in the practical joke. His was a personality which impelled admiration and affection in his colleagues and juniors. His originality and versatility were based upon quite extraordinary strength both of mind and of body, and it was this that enabled him to continue his contributions to humanity for so long a period.

J. F. GASKELL, M.D., F.R.C.P., D.P.H.

Dr. J. F. Gaskell, formerly senior physician at Addenbrooke's Hospital, Cambridge, died at his home in Cambridge, on September 11, aged 82.

Born on September 9, 1878, the son of W. H. Gaskell, M.D., F.R.S., the distinguished Cambridge physiologist, John Foster Gaskell was educated at Marlborough; Gonville and Caius College, Cambridge; and St. Bartholomew's Hospital. After graduating M.B., B.Ch. in 1907, he held a house appointment at Bart's and then became demonstrator in pathology at Leeds. Having been admitted M.R.C.P. in 1908, he took the D.P.H. in 1909, and proceeded M.D. in 1911, the year in which he was awarded a Beit Memorial Research Fellowship. Elected F.R.C.P. in 1914, he then served in the R.A.M.C., at first in the 1st Eastern General Hospital at Cambridge and then with the 41st General Hospital in Salonika. In 1920 he joined the honorary staff of Addenbrooke's Hospital as assistant physician and pathologist, becoming full physician in 1930, and retiring in 1946. He was president of the Cambridge Medical Society in 1938 and of the Cambridge and Huntingdon branch of the B.M.A. in 1945–6. His earlier work for the Association had been as an officer of the Section of Pathology and Bacteriology, first as secretary at the Annual Meeting in 1914 and then as a vice-president at the Annual Meeting in 1921.

L. C. M. writes: Gaskell's pathological training was reflected in his many publications, outstanding among which were the monograph on cerebrospinal fever, written jointly with the younger Michael Foster in 1916, and a Bradshaw Lecture given before the Royal College of Physicians on the pathology of pneumonia in 1927. Similarly, his views and teaching on clinical problems were founded on his wide pathological experience. He was a big man, both by physique and character. His courteous and scholarly manner at first sight suggested some austerity, but further acquaintance revealed the delightfully genial yet dogmatic disposition known to his friends. Gaskell did not engage in private practice, and his spare time was spent in his beautiful garden, which, happily, kept him fully occupied after retirement until a few months before his death. He did not enjoy social occasions and preferred to remain insulated from the outer world in his home and garden, but these were always open to his friends, who will always remember his welcome to them.

C. H. W. writes: I first met John Gaskell in 1923 when I joined him in his laboratory at Addenbrooke's Hospital. As physician and pathologist he had exceptional opportunities for studying medical problems, and the vista of subjects for investigation seemed unending. The rapidly expanding demand for new clinical pathological techniques, however, prevented most of the research on which he might have embarked. In spite of this he carried out some valuable investigations on pneumonia. For a man of outstanding ability he was simple in his tastes, devoid of ambition, old-fashioned, and with a strong dislike of innovations, especially the noisier sort. He was rightly held in great affection by his patients, and as he was himself a lover of the soil he probably understood the country folk better than a townsman would. As a colleague he was genial and tolerant, and beneath a slightly reserved manner lay a warmth of feeling and sympathy which was there for all who needed it.

E. K. MACDONALD, O.B.E., M.D., D.P.H.

Dr. E. K. Macdonald, medical officer of health of Leicester until his retirement a few months ago because of ill-health, died at Leicester Royal Infirmary on September 12, aged 64.

Ernest Kenneth Macdonald was born on February 12, 1896. He studied medicine at St. Thomas's Hospital, but before qualifying in 1919 he had served in the R.N.V.R. as a surgeon sub-lieutenant during the first world war and later he was promoted surgeon lieutenant in the Royal Navy. After qualification he held house appointments at St. Thomas's (where he was in the first Rugby fifteen), and thereafter decided on a career in public health. He took the D.P.H. in 1923 and proceeded M.D. in 1927.

After holding an appointment with the London County Council, he became deputy M.O.H. of Barnsley in 1926, M.O.H. of Keighley in 1929, of Barnsley in 1930, of Stockport in 1932, and of Leicester in 1935. He soon became known as an active and vigorous advocate of measures to protect and improve the health of the public. At Keighley, for instance, he organized a successful clean-milk campaign, and in later years he was a member of the Advisory Council to the Ministry of Works on building research and development. He had been a member of the Radium Commission, and from 1948 to 1951 he was chairman of the Central Council for Health Education. He served on numerous local committees connected with the Health Service and with voluntary work for the deaf and for the first-aid organizations.

A prominent member of the Society of Medical Officers of Health, he was a past-president of the County Borough Group, and when he was at Barnsley he was honorary secretary of the local Division of the B.M.A. He was appointed O.B.E. in 1942 and Honorary Physician to the Queen in 1953.

Dr. G. H. GIBSON writes: Dr. E. K. Macdonald was universally recognized as one of the leaders in the public-health field, and one who played an important part in the reshaping of the services as a result of the National Health Service Act. Although he had varied and extensive experience before coming to Leicester, it was his appointment in succession to the late Dr. Killick Millard as medical officer of health to that city in 1935 which brought him to the forefront, and it is as "Macdonald of Leicester" that he became so well known. He did much to maintain and improve the services in Leicester, especially in war time, but possibly the most notable contribution which he made to public health was the leadership he gave to the profession in the

years before and after 1948. At this time, when many medical officers of health were distressed at losing some of their services and were uneasy and despondent about the future, he was one of the few to foresee quickly the great opportunity that the Act brought, and some of his writings on that subject, including, especially, his presidential address to the East Midland Branch of the Society of Medical Officers of Health entitled "The Fragments that Remain," were inspiring at the time and make very good reading to-day.

Macdonald's reputation ensured that his advice was much in demand on a national as well as a local level. He was particularly interested in the Central Council for Health Education, of which he was, for a period, chairman, while he was a member of the Radium Commission and the Registrar-General's Advisory Committee. He was prominent in the Society of Medical Officers of Health, especially the East Midland Branch and the County Borough Group, in both of which bodies he served for a period as president. He took a prominent part in many local activities, especially those which had a strong element of social service. One of his particular interests was the Leicester and County Mission for the Deaf, of which he was chairman for some years, and his interest in the subject was shown by the fact that one of the first local authority clinics for the very young deaf child was established in Leicester in collaboration with the Ewings of Manchester. He was an enthusiastic and prominent freemason.

Macdonald was a man of distinguished appearance and strong personality. He held his opinions firmly, and expressed them freely, but never with any personal animosity to those who disagreed with him. He enjoyed discussion and argument, and with his variety of interests was a cheerful, stimulating, and entertaining companion. No appreciation of his life would be complete without some mention of the manner in which he overcame considerable handicaps in the way of ill-health. He had a serious illness at one stage in his life and suffered much from disabilities which very few people were allowed to realize. No word of complaint was ever heard from him, and it was possible this personal problem gave him such an insight into many problems in his professional work. He was a man of many friends, whose friendship he enjoyed, but he was never happier than in his own home with his wife and children and grandchildren. Our sincere sympathy is extended to his wife, whose support meant so much to him, and to his three daughters, two of whom are members of the medical profession.

JAMES RUSSELL, C.B.E., M.B., F.R.C.S.Ed. F.R.F.P.S.

Mr. James Russell, formerly senior surgeon to the Victoria Infirmary, Glasgow, died at his home in Newton Mearns on August 26. He was 80 years of age.

James Russell was born in 1880 at Busby, near Glasgow, the son of the headmaster of the local school, where he received his earliest education. Later he went on to Hutcheson's Boys School and Glasgow University, where he graduated M.B., Ch.B. in 1902. After holding house posts at the Victoria Infirmary and Belvidere Fever Hospital, he entered general practice near Glasgow. Some years later he decided to specialize in surgery, and was appointed a dispensary surgeon at the Victoria Infirmary, where he began a long association with the late R. H. Parry. He proceeded to the F.R.C.S.Ed. in 1909.

During the first world war he served in France, and came under the influence of the late Mr. Naughton Dunn and of the late Sir Robert Jones, and he came back to Scotland determined to encourage the newly developing specialty of orthopaedic surgery, which had received such a stimulus during the war. Appointed assistant surgeon to the Victoria Infirmary in 1919, he proceeded to full charge of wards a few years later. He built up an extensive surgical practice in Glasgow and the south-west of Scotland and at the same time pressed forward with his project of raising the standard of orthopaedic work. His efforts were crowned with success, for in the early 'thirties the first orthopaedic department in Scotland was opened at the Victoria Infirmary, and, in addition, a hospital was built at Philipshill, near Glasgow, to deal with convalescents and longer-term patients. He was a vice-president of the Section of Orthopaedics at the Annual Meeting of the B.M.A. in 1923, having before this served as honorary secretary of the Glasgow and West of Scotland Branch of the Association.

In the second world war Russell was appointed surgical director of the south-western area, and was responsible for the co-ordination of the medical services. He was appointed C.B.E. in 1945. He retired from hospital work in 1947, but remained as a very active member of the hospital management committee up to a few years ago, when a severe shock restricted his activities completely.

R. M. writes: With the passing of James Russell we bid farewell to a surgeon who exercised a great influence on the surgical life of Glasgow over a long period. It was the late Naughton Dunn who fired Russell with the enthusiasm for orthopaedic work. Naughton Dunn had been both house-surgeon and assistant to Sir Robert Jones, and it was through Dunn that Russell was introduced to Sir Robert and his work at Oswestry and Whitchurch. Returning to Scotland after the war, Russell quietly set about organizing support for an orthopaedic centre, securing the interest of industrialists, and attracting round him a small team of enthusiasts, of whom the late Alexander Miller, his successor in this work, was the most distinguished.

This orthopaedic department at the Victoria Infirmary and at Philipshill provided the nucleus upon which the orthopaedic services were built up in Scotland during the second world war.

Though interested above all in orthopaedic surgery, Russell remained a general surgeon, and as an operator he was deft, rapid, and with few frills. As a result of his training in general practice he remained very conservative in his outlook. James Russell had travelled abroad extensively, especially in America, and, seeing medicine as a whole, he strove to raise standards of hospital practice all along the line. He was largely instrumental in introducing specialist anaesthetists to the Victoria Infirmary in the late 'twenties, and in the 'thirties he frequently brought up the late Sir Archibald McIndoe to operate on selected cases in the hospital, and to arouse interest in plastic surgery. As a result, he was successful later in getting the first plastic surgery unit in Scotland established at Ballochmyle Hospital in Ayrshire.

James Russell was never self-seeking, but he was always planning ahead and was an obstinate fighter for what he thought was right. Consequently he was capable of inspiring enduring friendships and strong loyalties, but he also aroused at times lively and even bitter antagonisms. He was ever generous and helpful to young ability wherever he met it. He wrote little, but as a debater with a strong emotional appeal, both at medical meetings and in committee, he was unsurpassed.

Many who attended the Association of Surgeons or the Orthopaedic Association meetings before the second world war will recall his stocky figure, his whimsical humour, his streak of impish mischievousness, his fund of anecdote and story told in a rich Scottish idiom and in an accent which one faintly suspected of becoming more broad as he travelled south.

He was an enthusiastic fisherman when his busy life permitted, and a great lover of the countryside. The shock which immobilized him a few years ago left his mental faculties apparently unimpaired, and he was able to enjoy the company of his friends almost to the last.

To his daughter and son, a surgeon at Stirling, we extend our sincere sympathy.

G. EMRYS HARRIES, M.B., B.S., D.P.H.

Dr. G. Emrys Harries, consultant in infectious diseases to the Welsh regional hospital board and medical superintendent of Lansdowne Hospital, Cardiff, died on August 31 after a long period of ill-health. He was 61 years of age.

A native of Carmarthenshire, Gwilym Emrys Harries was born at Newcastle Emlyn on February 10, 1899. After service in the first world war, he went to St. Bartholomew's Hospital to study medicine. Qualifying in 1924, he graduated M.B., B.S. in 1927. After qualification he worked at the Joint Counties Mental Hospital, Carmarthen, but later decided on a public health career and took the D.P.H. in 1933. After holding the appointment of assistant medical officer of health to the Rhondda Urban District Council, he became, in 1934, medical superintendent of the Cardiff City Isolation Hospital and lecturer on infectious diseases at the Welsh National School of Medicine. After the inception of the National Health Service he was appointed consultant in infectious diseases to the Welsh regional hospital board.

An active member of the B.M.A., Dr. Emrys Harries was a member of the Welsh Committee at one time and served on the executive committee of the Cardiff Division and on the council of the South Wales and Monmouthshire Branch from 1940 to 1959. He had been honorary secretary of the Cardiff Division from 1949 to 1951 and vice-chairman in 1954–5, and he several times represented the Division at Annual Meetings of the B.M.A. He was also a past president of the Welsh Branch of the Society of Medical Officers of Health.

W. P. P. writes: Emrys Harries had a very strong personality and was one of the best-known consultants in Wales. He was an exceptionally good speaker in Welsh and English, and his ready wit always made him very much in demand as an after-dinner speaker. He had a remarkable memory, and it was always a delight to be in his company. His students will remember him for many years, particularly for his lucid explanations of his specialty and for the touch of humour he brought in even when dealing with clinical subjects. An exceptionally able clinician, he became well known throughout the country to all those working in "fevers." Especially notable were the good results he obtained in the treatment of cerebrospinal meningitis during the early stages of the second world war, and, later, in the treatment of tuberculous meningitis.

A prominent freemason, he was a past master of two lodges and a provincial grand lodge officer. He will be remembered particularly as a staunch friend, and he always had a great love of his native Welsh country and an intense loyalty to St. Bartholomew's Hospital. He is survived by his widow and two sons, the elder of whom is a lecturer in physiology at the Birmingham Medical School.

L. C. R. writes: Emrys Harries had a strong and striking personality, and his friends, colleagues, and patients are saddened at his absence from among us. His broad figure and cheerful countenance radiated kindliness, friendliness, and confidence, and his forthright and usually sound contributions to any discussion were major ones and advanced and accelerated the business of a meeting. As one of the founders of a local society of old students of the famous hospital of which he was a product, he was an indefatigable worker, making a great success of its annual reunion and dinner. He was one of the "ferment folk" and never a "passenger," and we shall miss him greatly.

Sir FRED BOWERBANK, K.B.E., M.D., F.R.C.P.Ed. F.R.A.C.P.

Sir Fred Bowerbank, consulting cardiologist to the Wellington Hospital, New Zealand, and formerly director-general of the medical services of the New Zealand Army and Air Force, died on August 25. He was 80 years of age.

Fred Thompson Bowerbank was born at Penrith, Cumberland, on April 30, 1880, and was educated at Penrith High School and Edinburgh University, where he graduated M.B., Ch.B. in 1904. Proceeding M.D. in 1917, he was elected a Member of the Royal College of Physicians of Edinburgh in 1925, and admitted a Fellow in 1929. In 1938 he was elected a foundation Fellow of the Royal Australasian College of Physicians. After graduation he first took an assistantship in Bury, Lancashire, then became senior house-physician at the Royal Free Hospital, London, and eventually joined a partnership at Walthamstow, becoming also medical officer at the Walthamstow Public Dispensary. In 1907, soon after his marriage to Miss Maud Pick, he went to New Zealand, settling at Wellington. For nearly fifty years he was on the staff of the Wellington Hospital, from 1912 to 1925 as honorary physician, and from 1925 to 1939 as honorary cardiologist. Since 1939 he had been consulting cardiologist to the hospital.

During the first world war he served with the 1st New Zealand Expeditionary Force, being five times mentioned in dispatches, and in 1917 appointed O.B.E. He was in Egypt in 1915–16, and then at No. 1 New Zealand General Hospital at Brockenhurst, in Hampshire, where he was in charge of the medical division. After the war he went back to his practice in Wellington, but in 1924 returned to the United Kingdom for postgraduate study.

Bowerbank was assistant director of medical services, Central Military District, New Zealand, from 1929 to 1934; director of medical services of the Army and principal medical officer of the Royal New Zealand Air Force from 1934 to 1939; and director-general of medical services of the Army and Air Force from 1939 to 1947. During his term of office as director-general he undertook an arduous tour of duty which took him to theatres of war all over the world. After the war one of his last duties as director-general was to prepare a report on the medical units in Japan, which he also visited. He retired in 1947 with the rank of major-general. He was Honorary Physician to the Governor-General of New Zealand from 1935 to 1939, and to the King from 1940 to 1948. In the 1946 New Year Honours he was appointed K.B.E., and later in the same year a Grand Officer in the Order of Orange-Nassau for his services to the Netherlands in the second world war.

He was vice-president and Dominion chairman of the Royal Australasian College of Physicians from 1944 to 1946. A member of the British Medical Association for fifty-four years, he was chairman of the Wellington Division from 1938 to 1940. He took an active part in the public life of Wellington, and for his services to the first-aid organizations he was appointed in 1946 a Knight of Grace of the Venerable Order of St. John of Jerusalem. In 1958 he published an autobiography entitled *A Doctor's Story*.

FREDERICK HALLIDAY, M.B., B.Ch., B.A.O.

Dr. Frederick Halliday, a well-known and respected general practitioner in Belfast, died on July 11.

Fred Halliday graduated M.B., B.Ch., from the Queen's University of Belfast in 1922, having served in the first world war in a special unit of the Royal Engineers drawn from the ranks of undergraduates and trained to deal with the use of gas by the enemy. After qualification, he set up an entirely new practice in the industrial area of east Belfast, and in a few years, by skill and intense application, developed it into a partnership of three, one of whom was his younger brother, Dr. John Halliday. For many years Fred Halliday served in the Royal Victoria Hospital, Belfast, as a clinical assistant on the medical side, and never failed to take the opportunities offered by modern diagnostic methods and therapeutics. Many patients and their families owe much to him for his conscientious approach in his care and management of them and of their illnesses. His professional skill and ability contained the essential constituents of erudition, gentleness, kindliness, and a profound sense of vocation.

H. I. McC. writes: The work of the British Medical Association in Northern Ireland for the past 20 years benefited much from the energy and wise counsel of Fred Halliday. In all the committees, investigations, and negotiations in which he played a part it was evident that he was devoting much of his life and energies in a sincere and fervent endeavour to do good for his colleagues. He had a flair for seeing the essentials of a problem and "gave counsel by his understanding." He was free from guile, malice, and the desire to dominate; of the highest character and principle, he was courageous in conception and in purpose. At all times he was a most valuable and reliable colleague.

Fred Halliday served us well in the years preceding and following the introduction of the National Health Service. He was joint honorary secretary of the Northern Ireland Branch in 1943, honorary secretary from 1944 to 1948, president in 1949–50, and the first chairman of the General Medical Services Committee (Northern Ireland) from 1950 to 1954.

His interests were many, and he was proud to have made a most valuable contribution to civil defence work in the last war. His main hobby was cabinet-making, and he pursued this with skill and diligence to produce many articles of furniture of grace and beauty. His home life was happy, with a wise and charming wife and four delightful children. Fred Halliday was intensely human and loved "to warm both hands before the fire of life." He reflected the natural kindness of his heart in his friendships, and I was proud to be the object of his friendship, confidence, and generosity for 30 years. Many phrases circulate in my mind when I think of Fred Halliday, but I suggest with pride and gratitude, "He was a good man, and a just."

G. F. BADER, B.M., B.Ch.

Dr. G. F. Bader, who was a ship surgeon serving with the Cunard Steamship Company, died suddenly on July 30. He was aged 51.

George Frederic Bader was born in South Africa on October 7, 1909. He won a Rhodes scholarship to University College, Oxford, where he was a rowing blue and also represented the university at swimming. Going on to Charing Cross Hospital, he graduated B.M., B.Ch. in 1943. During the second world war he served in the R.N.V.R. in H.M.S. *Loch Shin* and H.M.S. *Goodall*, and later at the Royal Naval Auxiliary Hospital, Woolton. Thereafter he was appointed senior registrar in the dermatological department of the Liverpool Royal Infirmary, having held similar posts at the Leicester and Bradford Royal Infirmaries. He joined the Cunard Steamship Company in 1959, and served as surgeon in the *Carinthia*, *Mauretania*, and *Caronia*.

R. M. H. writes: A person of distinguished bearing and possessing positive charm, G. F. B. was highly respected by passengers, officers, and crew alike. A great shot and a keen fisherman, he had an uncanny knack in the training of gundogs, and in gardening possessed to a wonderful degree "green fingers." On the evening of his arrival home from his last voyage in the *Mauretania*, prior to taking up another appointment in the *Britannic*, he remarked to his wife, a former nursing sister, that he had found in the practice of medicine at sea a most satisfying and rewarding experience to which he felt he could contribute much. His passing is acutely felt by his innumerable friends, who extend to his wife and children their deep sympathy.

T. G. MOORHEAD, M.D., LL.D., F.R.C.P. F.R.C.P.I.

The obituary of Professor T. G. Moorhead was published in the *Journal* of August 13 (p. 542).

W. R. writes: The passing of Professor Moorhead will revive memories in the hearts of old Dublin students all over the world. I knew him in the early nineteen-twenties when he was the leading physician in Dublin, and probably the greatest teacher of medicine in Ireland. The highest tribute I can pay him, nearly forty years later, is to say that his notes on materia medica, taken at lectures in those far-off days, are the only ones which I have not destroyed.

His lectures were memorable and never to be forgotten. Every point was illustrated by anecdotes from his rich experience—stories which echo in my ears even to-day. Students from every Dublin hospital would forsake their own wards to crowd his teaching round at Sir Patrick Dun's Hospital.

To be his house-physician was to occupy a post of distinction; fellow students would point you out as almost a superman. Moorhead arrived to do his morning round at a time when most physicians were eating their breakfast or reading their morning paper.

An Ulsterman by birth, he was impatient of sham and maybe sometimes a little abrupt. He seemed to be driven by a more powerful dynamo than most men, and not to possess a lazy bone in his body. The tragedy of his blindness only served to reveal the inner reserves of character and strength. When most men would have stepped down, Moorhead stepped up and marched forward through life with an even stronger step.

"Tommy" Moorhead, as students called him affectionately, will be remembered as one of the greatest teachers the Dublin School has ever known. As an old student I salute his memory with gratitude and affection.

F. GARFIELD HODDER WILLIAMS, O.B.E., LL.D. M.B., B.S.

The obituary of Dr. F. Garfield Hodder Williams was published in the *Journal* of August 20 (p. 608).

Lieutenant-Colonel H. H. KING, C.I.E., writes: I would like to add my tribute to the memory of Dr. Garfield Hodder Williams. "Hodder," as I called him at Bart's, was a truly great man, great in greatness of soul and purpose. His friendliness, cheerfulness, and clean Christian life were a help and inspiration to all his friends. He did magnificent work for our Bart's Christian Union, of which for a time he was honorary secretary. We thank God for him and rejoice in the memory of him.

MARJORY W. WARREN, C.B.E., M.R.C.S., L.R.C.P.

The obituary of Dr. Marjory Warren was published in the *Journal* of September 17.

Lord AMULREE writes: I first met Marjory Warren at the end of the war, when I visited her at the West Middlesex Hospital. Like others, I was fascinated by the work she was doing and impressed by the modest way in which she explained to me how simple it all was. When she took over the old chronic sick wards in the public assistance institution in 1935 she had been amazed, as well as angered, to find that to the care of this type of sick people ordinary medical standards and principles did not apply: as is now well known, she soon changed all that.

Later on we worked together, with four or five others, on the formation of the Medical Society for the Care of the Elderly—now the British Geriatric Society—and our friendship continued until her untimely death on September 5.

Marjory Warren worked hard, and expected her staff—and her patients—to work hard, too. As a result, her success was great. She was always ready to show visitors round her wards, and they came in great numbers; she was as willing to learn from them as to teach them her own methods. Her visit to Australia gave her great satisfaction, while she felt that her recent award of the C.B.E. was more a tribute to the importance of geriatrics than to her own work—although it was to her work that the general interest in the rehabilitation of the elderly chronic sick is due. And many ill persons who do not really fall into this category have cause to thank her for the great work that she started. Marjory Warren was a stimulating and entertaining companion, as

well as a loyal and true friend: we shall all miss her spirited and apposite interventions at meetings of the British Geriatric Society and other bodies.

Medico-Legal

NOTIFICATION OF INFECTIOUS DISEASE

[FROM OUR LEGAL CORRESPONDENT]

The failure of a local doctor to give immediate notification to the Medical Officer of Health of a case of typhoid was the subject of a report of the Skegness Public Health Committee considered by the Urban District Council on August 24 (*Yorkshire Post*, August 25). The doctor concerned was allowed to speak on his own behalf at the meeting of the Urban District Council in reply to the report of the Public Health Committee. He apologized for not adhering to the strict letter of the law, but said that, as the patient was being treated in hospital in a manner which satisfied the isolation requirements of a case of the enteric group of diseases, the date of notification did not seem to be so important. By the date of the council meeting the incubation period had expired and no further case of typhoid had been reported within the urban district. The Public Health Committee did not recommend prosecution of the doctor, but both they and the Council took a serious view of his conduct, and resolved that the attention of other doctors in the district should be drawn to their obligations in this respect.

Obligation to Notify

When an inmate of any building used for human habitation, not being a hospital in which persons suffering from an infectious disease are received, is suffering from a notifiable disease, certain obligations devolve upon both the occupier of the building and the medical practitioner in attendance, under the Public Health Act, 1936. The practitioner must send to the local medical officer of health a certificate stating the name of the patient, the situation of the building, and the disease from which in his opinion the patient is suffering. The medical practitioner must do this "as soon as he becomes aware that the patient is suffering from a notifiable disease."[1] The local authority is under a statutory obligation to supply forms of certificate free of charge, and must pay the medical practitioner a fee for every certificate made by him (2s. 6d. if the case occurs in his private practice: 1s. if it occurs in his practice as medical officer of any public body or institution).[2] The maximum penalty for failure to send a certificate as required is a fine of not more than £2.

The word "hospital" in the Act includes any premises for the reception of the sick, but the qualifying words in Section 144 make it clear that the practitioner in attendance on a patient in hospital must report notifiable diseases discovered there if the hospital does not normally treat infectious diseases. Where a case of notifiable disease occurs in a building occupied by H.M. Forces there is still an obligation to report to the local medical officer of health.[3] Special provision has been made for the notification of infectious diseases contracted by members of visiting Forces.[4] The list of notifiable diseases is, no doubt, well known to the profession, but amendments by later regulations make the position a little confusing. Local authorities also may, with the approval of the Minister, declare further diseases notifiable in their areas. There is a separate statutory provision dealing with the notification of diseases in London,[5] though some statutory regulations apply both to London and to the rest of the country.

[1] Public Health Act, 1936, s. 144.
[2] Ibid., s. 145.
[3] Ibid., s. 146.
[4] Visiting Forces (Application of Law) Order, 1954, S.I. 1954, No. 635, art. 14(1).
[5] Public Health (London) Act, 1939, s. 192.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **September 3** (No. 35) and corresponding week 1959.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1960					1959				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	2	0	1	2	0	1	0	3
Dysentery	354	33	163	21	2	387	28	253	7	1
Encephalitis, acute	3	1	0	0		4	0		0	
Enteric fever:										
Typhoid	7	2	0	0		6	0	0	2	2
Paratyphoid	6	3	0	0		42	4	1 (B)	0	
Food-poisoning	197	7	15	5		415	34	36	3	
Infective enteritis or diarrhoea under 2 years				18	25				14	58
Measles*	1,398	61	47	4	8	1,236	43	14	24	32
Meningococcal infection	10	1	14	1	1	13	2	24	0	
Ophthalmia neonatorum	22	1	3	0		29	3	7	0	1
Pneumonia†	105	7	90	3		101	9	90	3	1
Poliomyelitis, acute:										
Paralytic	9	5	0	} 0	3	{ 26	3	1	} 0	2
Non-paralytic	7	0	2			18	3	2		
Puerperal fever§	181	28	11	1		178	38	13	0	
Scarlet fever	169	7	35	9	8	248	248	58	9	13
Tuberculosis:										
Respiratory	345	35	84	12		377	39	60	14	
Non-respiratory	55	3	12	3		52	7	5	7	
Whooping-cough	1,416	131	131	7	26	873	42	191	7	48

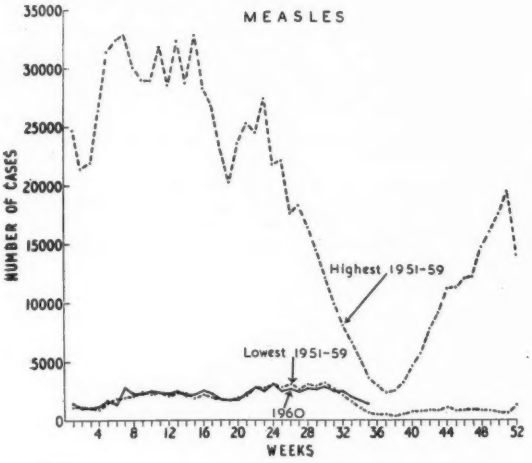
DEATHS	1960					1959				
	Eng. & Wales	Lond.	Scot.	N. Ire	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	0	0	0	0	0	0
Dysentery	0	0		0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	3	0	2	0	0	8	0	1	0	2
Influenza	6	0	0	0	0	7	1	1	0	0
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		0	0				0	0		
Pneumonia	371	29	19	15	3	286	22	13	4	1
Poliomyelitis, acute	0	0		0	1	0	0		0	0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	} 71	{ 3	3	0	3	} 70	{ 6	5	2	3
Non-respiratory		0	1	0	0		0	0	0	0
Whooping-cough	0	0	0	0	0	0	0	0	0	0
Deaths 0–1 year	270	31	25	7	11	248	20	22	5	6
Deaths (excluding stillbirths)	8,196	635	509	100	146	7,436	577	481	110	114
LIVE BIRTHS	14,636	1242	990	261	331	13,984	1193	926	234	388
STILLBIRTHS	276	27	21			278	20	23	6	

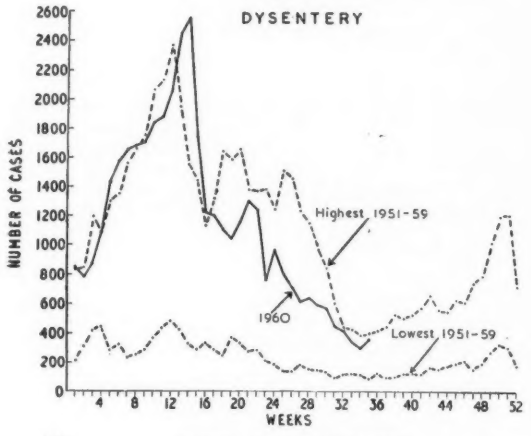
* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

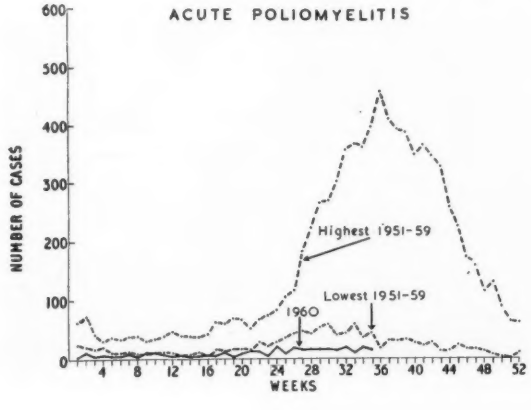
Vital Statistics

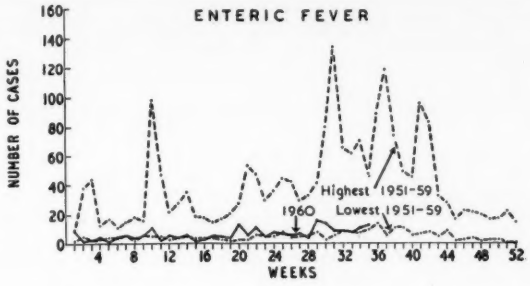
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1951–9 are shown thus ------, the figures for 1960 thus ———. Except for the curves showing notifications in 1960, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Venereal Diseases

In England and Wales during the quarter ending March 31, 1960, 970 new cases of syphilis were reported by the clinics, compared with 980 in the previous year. Of these, 242 were classified as primary, secondary, or latent in the first year of infection. Two cases of congenital syphilis in children under 1 year were reported, and 95 cases in persons over that age. New cases of gonorrhoea (with corresponding 1959 figures in parentheses) numbered 7,291 (6,304), of chancroid 42 (64), and of non-gonococcal urethritis (males only) 4,590 (3,993).—*Monthly Bulletin of the Ministry of Health*, August, 1960.

Infectious Diseases

Areas where numbers of notifications were high in the latest two weeks for which figures are available.

	Week Ending	
Acute Poliomyelitis	Sept. 3	**Sept. 10**
Warwickshire	2	**2**
Birmingham C.B.	2	**2**
Lincolnshire	0	**2**
Dysentery		
Cheshire	15	**24**
Hoylake U.D.	0	**18**
Essex	21	**25**
Saffron Walden M.B.	0	**11**
Kent	10	**17**
Deal M.B.	4	**15**
Lancashire	69	**71**
Blackburn C.B.	2	**16**
Liverpool C.B.	19	**22**
Wiltshire	0	**22**
Pewsey R.D.	0	**18**
Yorkshire West Riding	52	**46**
Leeds C.B.	43	**14**
Glasgow	123	**111**
Food Poisoning		
Cornwall	0	**25**
Truro R.D.	0	**25**

Universities and Colleges

QUEEN'S UNIVERSITY OF BELFAST

At a Summer Graduation ceremony on July 6 the following degrees were conferred:

M.D.—W. M. Darling, C. Levene, T. J. M. Myles, R. W. Whiteley.

M.B., B.Ch., B.A.O.—P. H. C. Ashby, B. E. Beattie, J. E. Black, Eileen E. Blackstock, C. H. Blake, J. G. Bradley, B. D. Burrows, D. G. Campbell, J. J. Campbell, Karin A. Clauss, D. L. Coppel, D. R. Delargy, C. J. Dick, C. Dubovy, W. J. Gamble, D. T. Gray, P. B. Halmos, N. G. Hamilton, B. G. Hayes, H. O. Kane, Rosaline Kelly, R. F. A. Lynas, V. P. Lynch, S. M. Lyons, C. McCafferty, M. M. W. McCauley, V. R. McCready, J. McCurdy, J. B. McGucken, Sadie S. McIlroy, J. F. McKenna, A. McKibbin, J. G. McNulty, Alison C. McWilliam, S. A. Marshall, C. J. H. Mitchell, W. G. V. Mitchell, Yvonne G. Morton, T. F. B. Murphy, H. B. Murtagh, Mary L. Naylor, J. K. Nelson, N. C. Nevin, A. E. S. Rainey, H. A. Richter, J. A. Rudis, Esther M. Rutledge, H. Sinanan, P. Smith, Mary S. Sprott, Mary A. Thompson, G. Vaccaro, J. B. W. Walmsley, Ena Wilson.

Medical News

W.H.O. in the Congo

A report on the Congo from the W.H.O. Regional Office for Africa, dated September 7, states that the medical care services there have suffered less than the preventive health services from the exodus of European medical personnel. There are widespread reports of small localized outbreaks of smallpox, and in some areas vaccination has not been carried out for some considerable time. In most areas Congolese staff are continuing the routine treatment of leprosy, though some patients are leaving institutions and returning to their villages. The number of cases of malaria and filariasis is stated to be rising. W.H.O. has placed its medical recruitment service at the disposal of the Congolese Government. According to the report 10 governmental medical teams (from Ghana, Switzerland, Israel, and U.S.S.R.) and 23 national Red Cross or Red Crescent teams are operating in the Congo. Together these provide 79 doctors. Australia and Canada have each provided two of the latter teams, and India, Pakistan, and Ireland one each.

First Aid in Factories

From July 1, 1961, first-aiders in factories with more than 50 workers must be registered nurses, enrolled assistant nurses, or holders of first-aid certificates issued within the immediately preceding three years by the St. John Ambulance Association, the St. Andrew's Ambulance Association, or the British Red Cross. These requirements are embodied in an order (S.I. 1960, No. 1612) issued by the Minister of Labour on September 13, under Section 19 (First Aid) of the Factories Act, 1959. The commencing date of Section 19 is laid down in S.I. 1960, No. 1611.

Flatlets for Old People

The Minister of Housing and Local Government, Mr. HENRY BROOKE, has written to local housing authorities (Circular No. 47/60), urging those that have not yet built flatlets for old people to review their building programmes so as to do so. The circular states that those completed have proved a great success. "(They) have shown conclusively that flatlets are, for many old people, the best way of providing them with comfortable homes of their own, which at the same time cater for their special needs."

New Block at Gogarburn Institution

One of two residential villas for male low-grade mental defectives has recently been completed at Gogarburn Institution, Corstorphine, Edinburgh.

The villa, flanked on the north by the Gogar Burn and on the east by a belt of trees, houses 60 patients. There are living-rooms where they can enjoy television and wireless programmes and receive visitors. In the dining-room the patients are seated not in long rows but at tables for six. They sleep in two dormitories, and two single rooms are provided for the use of selected patients. (Architect: JOHN HOLT, regional architect, S.E. Regional Hospital Board, Scotland.)

Toxic Chemicals Research Group

Professor R. E. LANE, Nuffield professor of occupational health at Manchester University, has been appointed to the Research Study Group on Toxic Chemicals used in Agriculture and Food Storage in succession to Dr. D. HUNTER, who has resigned.

New Name for "A.M.A. Archives of Industrial Health"

The title of the *A.M.A. Archives of Industrial Health* has been changed to *Archives of Environmental Health*, with the subtitles of Preventive Medicine, Industrial Health, and Aerospace Medicine. "A.M.A." has been dropped from the title of all ten special journals published by the American Medical Association.

Booklet on Cerebral Palsy

Cerebral Palsy, a memorandum which has been prepared for the Central Health Services Council and the Minister of Health by the Standing Medical Advisory Committee, is to be distributed through Executive Councils to all practitioners providing general medical services in the National Health Service. Copies are also being sent to medical officers of health.

It offers information concerning incidence, early recognition of the condition during infancy; provision available for full assessment, treatment, and training of children; the difficulties and needs of young persons; and the problems of the older groups.

Conjoined Twins at Bart's

Two 4-month-old twin girls, joined by the tops of their heads, have been transferred from the Bon Secours Hospital, Cork, to St. Bartholomew's Hospital, London, for investigation and possible separation. The twins were delivered two months prematurely by caesarean section.

Mortuary Attendant's Discovery

A mortuary attendant was the first to discover a stab wound through the heart of a woman who was dead when admitted to the Nottingham General Hospital the previous evening. A man has been charged with her murder. (*The Times*, September 15.)

Changes of Address

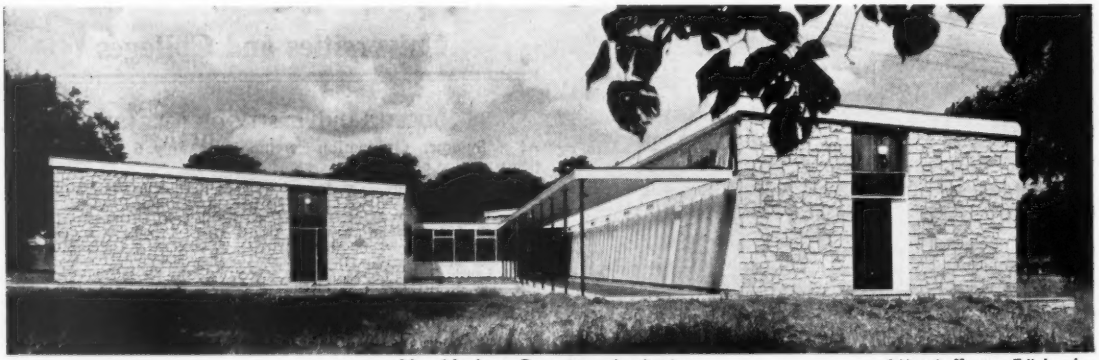
From October 1 the address of the International Hospital Federation will be 24–26 London Bridge Street, London S.E.1—a historic site, as it was here that the early St. Thomas's Hospital stood.

The headquarters of Remploy Ltd., the national organization employing those who are severely disabled, will move to a new six-story building, Remploy House, 415 Edgware Road, London N.W.2, on October 3.

People in the News

Dr. J. A. MILNE has been appointed McCall Anderson lecturer in dermatology at Glasgow University. He will be in charge of the dermatological department at the Western Infirmary, Glasgow.

Dr. PHILIPPE BAUWENS, physician-in-charge, department of physical medicine, St. Thomas's Hospital, has been presented with the Gold Key Award of the American



New block at Gogarburn Institution. [*Alastair Hunter, Edinburgh*

Congress of Physical Medicine in recognition of his contributions in this field.

Dr. R. J. GOLDACRE, Ph.D., has been appointed to the London University readership in cell physiology, tenable at the Institute of Cancer Research, Royal Cancer Hospital.

COMING EVENTS

William Meredith Fletcher Shaw Lecture.—Dr. T. F. Corkill will lecture on "New Zealand's Debt to British Obstetrics," September 23, 5 p.m., at the Royal College of Obstetricians and Gynaecologists. Tickets from the Secretary of the College.

Middlesex Hospital Medical School.—Week-end course for former Middlesex men, September 30 (starting 2.15 p.m.) —October 2. Annual dinner at the Savoy Hotel (7 for 7.30 p.m.), September 30. Further information from the Medical School Secretary, the Middlesex Hospital, London W.1.

Institute of Diseases of the Chest.—Clinical demonstrations, open to medical practitioners without fee, in the lecture room of the Institute (in the grounds of the Brompton Hospital, Fulham Road, London S.W.3) on Fridays at 5 p.m. from September 30 to December 16.

Cambridge University Medical School.—Details of postgraduate courses for general practitioners during the academic year October 1, 1960, to July 31, 1961, are now available from the Secretary, the Medical School, Tennis Court Road, Cambridge.

Medical Faculty, Birmingham University.—Mr. L. FARRER-BROWN will deliver the inaugural address at 3 p.m. on October 3.

Medical Defence Union.—Annual general meeting, 3.15 p.m. on October 4 at Tavistock House South, Tavistock Square, London W.C.1.

Royal Free Hospital School of Medicine.—Inaugural address: Sir IFOR EVANS, October 5, 3 p.m., at the Senate House, London W.C.1.

Symposium on Cancer.—Week-end course, October 14–15, for consultants, S.H.M.O.s, and senior registrars, on recent advances in treatment, diagnosis, and research on cancer. Tickets (free) and information from the secretary, Institute of Cancer Research, Royal Cancer Hospital, 33 Sumner Place, London S.W.7.

Faculty of Radiologists.—Provincial meeting in Cardiff, October 15. Details from the Faculty, 47 Lincoln's Inn Fields, London W.C.2.

British Postgraduate Medical Federation.—Professor C. H. WADDINGTON, F.R.S., will deliver the inaugural lecture of the 1960–1 series on the Scientific Basis of Medicine on October 20 at 5.30 p.m., at the Senate House, London University. His subject will be "The Significance of Developmental Biology."

Harben Lectures.—Professor R. A. KEHOE, department of preventive medicine and industrial health, Kettering Laboratory, Cincinnati University: "The Metabolism of Lead in Health and Disease." Three lectures, October 25, 26, 27, all at 5 p.m. Details from Royal Institute of Public Health and Hygiene, 28 Portland Place, London W.1. Admission free.

Sydney Watson Smith Lecture.—Sir STANLEY DAVIDSON will lecture on "Anaemia and Operations on the Gastro-intestinal Tract" at the Royal College of Physicians of Edinburgh on October 26 at 5 p.m.

Wessex Rahere Club.—Autumn dinner, October 29, at the Grand Spa Hotel, Clifton, Bristol. Details from Mr. A. Daunt Bateman, F.R.C.S., 11 The Circus, Bath.

Conference on Accident Surgery.—Details of a conference, November 30 to December 2, arranged jointly by the University of Glasgow and the Royal Faculty of Physicians and Surgeons, are given at p. 64 of the advertisements.

University College Hospital Medical School.—Programme of postgraduate demonstrations, October 27, 28, including annual dinner, Savoy Hotel, Strand, London W.C.2, October 28, 7 for 8 p.m. Details from Honorary Secretary, U.C.H. Old Students' Association, University Street, London W.C.1 (Tel. EUS 5861).

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Thursday, September 29

LONDON JEWISH HOSPITAL MEDICAL SOCIETY.—At 11 Chandos Street, W., 8.30 p.m., presidential address by Dr. David Preiskel: Physiotherapy.

Friday, September 30

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. J. Smart: clinical demonstration.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—3.30 p.m., clinical discussion for general practitioners. Mr. A. S. Walker: Prescription of Hearing-aids.

SOCIETY OF CHEMICAL INDUSTRY: FINE CHEMICALS GROUP.—At Alderley Park, Cheshire, 2 p.m., symposium: Drugs for the Treatment of Hypertension.

Saturday, October 1

CAMBRIDGE UNIVERSITY MEDICAL SCHOOL.—At Lecture Room "B," Addenbrooke's Hospital, Symposium on Haematology. Morning: 10.30 a.m., Dr. D'A. Kok: Clinical Diagnosis of Blood Disorders; 11.30 a.m., Dr. D. G. Chalmers: Use of Laboratory Services in Haematology for the General Practitioner; 12.15 p.m., Dr. F. G. J. Hayhoe: Treatment of Common Anaemias. Afternoon: 2.30 p.m., Dr. E. Davidson: Investigation and Treatment of Haemorrhagic Diseases; 3.30 p.m., Dr. C. B. V. Walker: Practitioner and the National Transfusion Service.

NORTH-EAST METROPOLITAN THORACIC SOCIETY.—At Papworth Hall, Cambridge, 10.30 for 11 a.m., joint meeting with East Anglian Thoracic Society. Papers by Dr. Audrey Hanson, Dr. R. A. Bruce, Dr. D. J. Lawless, and Dr. H. A. Fleming.

NORTH OF ENGLAND OTOLARYNGOLOGICAL SOCIETY.—At Bolton, 2 p.m., 14th annual and 40th ordinary meeting.

APPOINTMENTS

NORTH-WEST METROPOLITAN REGIONAL HOSPITAL BOARD.—A. E. Carter, M.B., B.S., F.R.C.S., Consultant Surgeon, King Edward Memorial Hospital and Clayponds Wing; D. E. Bolt, M.B., Ch.B., F.R.C.S., Consultant Surgeon, West Middlesex and South Middlesex Hospitals; Dinah C. M. Henderson, M.B., Ch.B., D.M.R.D., Consultant Radiologist, Edgware General and West Hendon Hospitals; D. R. Sweetnam, M.B., B.Chir., F.R.C.S., Consultant Orthopaedic Surgeon, King Edward Memorial Hospital (including Clayponds Wing); A. E. Richardson, M.B., B.S., F.R.C.S., F.R.C.S.Ed., Consultant Neurosurgeon, Whittington Hospital; J. F. Hare, M.B., Ch.B., M.R.C.P., Assistant Physician (consultant grade), Windsor Group Chest Clinic and Canadian Red Cross Hospital; K. Bobath, M.D., D.P.M., Consultant Psychiatrist, Harperbury Hospital (new Cerebral Palsy Unit).

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Porteous.—On September 6, 1960, at Liverpool Maternity Hospital, to Myfanwy (formerly Dr. Roberts), wife of Dr. Colin Ross Porteous, a son.

DEATHS

Bendle.—On August 27, 1960, at his home, 20 Littlemoor Road, Preston, Weymouth, Dorset, William George Bendle, M.B., F.R.C.S.Ed.

Black.—On August 20, 1960, the result of a road accident, Alfred Black, L.R.C.P.&S.Ed., L.R.F.P.S., of 7 Beresford Drive, Woodford Green, Essex, formerly of 97 Browning Road, Manor Park, London E.

Eckford.—On August 21, 1960, at The Rosery, Garfit's Lane, Boston, Lincs, Alan Eckford, M.D., D.Obst.R.C.O.G.

Graetz.—On August 16, 1960, at Woodside Road, Lockwood, Huddersfield, Gerhard Herman Arnold Graetz, M.B., B.Ch., aged 56.

Grant.—On August 20, 1960, Montagu Frederick Grant, M.D., D.P.H., Colonel, late R.A.M.C., retired, of Bredon House, Bredon, Tewkesbury, Glos, aged 82.

Hutchinson.—On August 22, 1960, at Whipps Cross Hospital, London E., Michael Lincoln Hutchinson, M.R.C.S., L.R.C.P., aged 59.

Hyman.—On August 22, 1960, Morris Hyman, M.B., Ch.B., of 34 Cedra Court, London N.

Neville.—On August 16, 1960, at Hill End Hospital, St. Albans, Herts, Norman Alan Neville, B.M., B.Ch., M.R.C.P., of 9 Westfield Road, Hertford, Herts, aged 46.

Oxley.—On August 17, 1960, in Kent and Canterbury Hospital, James Charles Stewart Oxley, F.R.C.S.Ed., Lieutenant-Colonel, I.M.S., retired, of 138 Dover Road, Walmer, Kent.

Pennington.—On August 19, 1960, at the Memorial Hospital, Henley-on-Thames, Oxon, Drury Pennington, M.B., B.Ch., aged 85.

Pike.—On August 26, 1960, at the Queen Elizabeth Hospital, Birmingham, Warwicks, John Donald Pike, M.B., Ch.B., of Applebeck, Streetsbrook Road, Solihull, Birmingham.

Primrose.—On August 16, 1960, at Dalchalm, Brora, Sutherland, Dorothy Anderson Primrose, M.B., Ch.B.

Richardson.—On September 16, 1960, at his home, The Holt, Gerrards Cross, Bucks, Sir Albert Victor John Richardson, K.B.E., C.B., M.B., B.Ch., D.P.H., Air Marshal, R.A.F., retired, aged 76.

Robertson.—On August 24, 1960, at Ravenswood, Whalley, near Blackburn, Lancs, Guy Scott Robertson, M.B., Ch.B., aged 60.

Russell.—On August 26, 1960, at Kirkhill Cottage, Newton Mearns, Renfrewshire, James Russell, C.B.E., M.B., F.R.C.S.Ed., F.R.F.P.S., late of Glasgow.

Symons.—On August 20, 1960, at King Edward VII Hospital, Windsor, Berks, William John Francis Symons, M.B., B.Ch.

Woodhouse.—On August 18, 1960, at Plymouth, Devon, Guy Walker Woodhouse, M.R.C.S., L.R.C.P., Surgeon Captain, R.N., retired.

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Chlorination of Swimming-baths

Q.—*Is there any risk of direct chemical damage to the conjunctiva or of causing increased susceptibility to local infection when water in a swimming-bath is over-chlorinated?*

A.—Over-chlorination, although causing slight discomfort, is unlikely to cause any significant damage to the eyes, and there is no evidence to suggest any increased susceptibility to local infection.

Monilial Vulvitis and Carcinoma

Q.—*Is there a risk of malignant changes occurring in pruritus vulvae due to chronic intestinal moniliasis?*

A.—Intestinal moniliasis does not usually cause pruritus vulvae unless it results in infection of the vulva itself. A special association between monilial vulvitis and carcinoma is not described. Nevertheless, some authorities take the view that any long-standing skin lesion of the vulva, and especially one which causes scratching, can ultimately result in malignant change. Considering the frequency of pruritus vulvae and the rarity of carcinoma vulvae the risk, however, must be small.

Excluding Noise

Q.—*Is there an ear-plug or any other appliance which is more effective in excluding noise than cotton-wool packed into the external auditory meatus?*

A.—Yes, there are many. First, there are many proprietary makes of ear-plugs on the market. These are made in a variety of materials—rubber, plastic (soft or firm), and even metal. They are worn by insertion into the exterior auditory meatus. Secondly, there are several ear-defenders designed for and used in noisy industries, including aviation, when it is associated with jet aircraft engines. These are worn like earphones and have large ear-encasing acoustic domes with malleable or fluid-filled rims. Thirdly, there is the so-called "bone dome" used by Service and certain civil aircraft pilots. This consists of a rigid helmet encasing the head with special ear-protecting pads.

Contact with Leprosy in Infancy

Q.—*A baby was separated from his mother at the age of 10 days and was taken into an institution. During the 10 days he was breast-fed. Three months later the mother was found to have leprosy. Bacilli were found both in her nasal secretions and in the blood around her skin lesions. So far as it can be assessed, there were no suspicious signs until two and a half months after delivery. The baby, now aged 6 months, is clinically normal. Is it possible to forecast the baby's future? What investigation should be done, and is any prophylactic treatment necessary?*

A.—While it is claimed that children are more susceptible to leprosy than adults, the incidence of leprosy amongst children who have been separated from infective parents before they were 6 months of age is so extremely rare that it can be taken that the chances of a child acquiring the disease after having been separated from an infective mother at 10 days is so infinitesimal that the risk can be discounted. So far as I know, there are only two cases on record in which leprosy has been described in children under 6 months. It must be remembered that the natural immunity to leprosy is very high indeed, and that even when children have been kept with an infective mother for as long as eighteen months the incidence of leprosy in the child is again very low. Therefore so far as this child is concerned I do not think there is any cause for concern.

With regard to the possibility of forecasting the baby's future acquirement of the disease, this would be very difficult. All one can say is that the average latent period in leprosy is one to three years, and if no signs of the disease have appeared within a period of five years one can conclude, I think, that the child would not show any signs of infection in later life.

With regard to possible investigations, workers in Bombay have found that in certain instances evidences of an early infection can be demonstrated in contacts of open cases of leprosy. An investigation that could be done would be to take a small biopsy from the skin of the back of the child and have it fixed under what is termed the hyalase technique. The area to be biopsied is injected intradermally with procaine and hyalase (1 ampoule of crystalline hyalase to 2 ml. of procaine). Then the physician waits not less than 10 minutes and not more than 20 minutes and performs a small biopsy. The tissue then is fixed in neutral formalin and despatched to a laboratory, where special investigations can be undertaken with reference to the condition of the nerves in leprosy. But the chances of any definite evidence of infection are so slight that I think that this is hardly worth while.

I would not recommend any prophylactic treatment, for in this case it would mean a course of treatment which should extend for a period of five years—that is, until the child is 5. A prophylactic dose of sulphones in a case of this type would be 10 mg. dapsone (diamino-diphenyl sulphone) twice a week for one month, then 25 mg. of dapsone twice a week until the child is aged 5. Then all treatment could be stopped. A step which could be taken would be to vaccinate the child with B.C.G., since it is generally considered that a positive lepromin reaction is more valuable than a negative. It is probably impossible to secure lepromin in this case, and therefore I would suggest that the child be vaccinated with B.C.G.

Finally, I think, because of the extreme rarity of infection at so low an age, that apart from examining the child every six months for the next three to five years no further steps need be taken.

A leading article on modern treatment of leprosy was published in a recent issue of the *Journal* (August 27, p. 655).

Up on the Points

Q.—*At what age should a child learning ballet dancing be allowed to "go up on her points"? Is it likely to be inadvisable in a child aged 10?*

A.—I do not think that we know the answer to this. I personally cannot see any reason for setting an age limit, and I am sure 10 years of age would be quite safe.

Collected Articles from the "British Medical Journal"

The following books are available through booksellers or from the Publishing Manager, B.M.A. House. Prices, which include postage, are now the same for both inland and overseas.

Refresher Course for General Practitioners, Volume 3 (26s. 9d.).
Clinical Pathology in General Practice (22s. 3d.).
Any Questions?, Volume 3 (8s. 3d.).

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